Exhibit F

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IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

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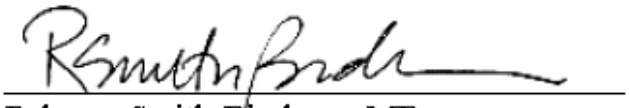

Rebecca Smith-Bindman, MD

The Relationship Between Exposure to Perineal Talc Powder Products and Ovarian Cancer

Expert Report

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I. Executive Summary

Substantial evidence supports a strong positive association between ovarian cancer and genital exposure to talcum powder products and that regular exposure to talcum powder products causes ovarian cancer in some women. Talc is a naturally occurring mineral used in cosmetic products because of its desirable chemical properties such as being soft and absorbent. Women who have had regular exposure of the genitals (specifically the perineal region from the pubic area to the anal area) to talcum powder products are at increased risk of developing invasive ovarian cancer, in particular serous cancer, the most common and most lethal form. In the United States, a substantial portion of women report having ever used talc powder products at some point in their life. The most commonly reported frequency of talcum powder product use is daily. Women who use talcum powder products daily increase their risk of developing ovarian cancer significantly. Regular exposure causes ovarian cancer in some women.

I was asked to review the medical and scientific literature regarding the relationship between genital talcum powder product use and ovarian cancer and determine whether the relationship is causal. For this extensive analysis and report, I applied the same methodology with the same scientific rigor that I use in my research and clinical practice. I reviewed 43 relevant publications presenting scientific data on the association between ovarian cancer and exposure to talc powder products: 4 cohort studies, 8 systematic reviews, 2 studies that pooled data from multiple individual studies, and 30 case-control studies. I also read numerous review articles, and systematic reviews on related topics such as those completed by the International Agency on Research on Cancer (IARC). I also completed my own, new systematic review on of the studies that I reviewed as part of this report. This report contains my overview of these publications plus a detailed new systematic review of the studies that I conducted. After reading, evaluating, and summarizing these publications, in my expert opinion, I do not have any uncertainty that regular exposure to talc powder products increases a woman's chance of developing epithelial ovarian cancer. In my expert opinion, regular exposure to talcum powder products causes ovarian cancer

Quantifying the precise magnitude of the association is more difficult than establishing the association. The association will certainly vary by demographic and reproductive factors and whether women have other underlying ovarian cancer risk factors and exposures. With that caveat, **it is my opinion that women exposed to perineal talc powder products on a regular basis have about a 50% increase in their subsequent risk of developing invasive serous ovarian cancer**, compared to women who do not regularly use talc and even after accounting for other ovarian cancer risk factors. This estimate is supported by existing publications and my quantitative review of the scientific literature that focused on summarizing studies that addressed regular exposure to talc powder products as a risk factor for epithelial ovarian cancer, and in particular serous cancer. Talcum powder exposure is associated with other epithelial cancer subtypes (in particular, clear cell and endometrioid carcinoma), but because these cancers are less common, and because fewer studies have evaluated these cancers in sufficient numbers, quantifying the associations is more difficult. While some publications estimated talc powder products have a slightly greater risk of these cancer subtypes, others

estimated a slightly lower risk of these cancer subtypes. In my opinion, this risk is likely overall in about the same range as for serous cancer, but I would estimate slightly less at 40% increased risk.

The epidemiological evidence documents a strong, positive association between exposure to talcum powder products and ovarian cancer and that regular exposure causes ovarian cancer. The epidemiological evidence alone does not confirm the mechanism by which talc powder product increases ovarian cancer risk, nor does it confirm the specific component in talcum powder products that makes it carcinogenic. Nonetheless, the literature provides compelling evidence that exposure to talcum powder products leads to chronic inflammation and that the inflammation induces a strong biological response that results in the induction, promotion, and growth of cancer. Further, there is evidence that several highly carcinogenic agents are components of the talcum powder products. These include, most importantly, asbestos, a Group 1 carcinogen that the International Agency for Research on Cancer (IARC) has determined causes ovarian cancer. I have seen evidence that talcum powder products contain asbestos. Second, talcum powder products contain asbestiform talc particles which have a similarity in structure to asbestos fibers (and which IARC concludes are carcinogenic). Lastly, talcum powder products contain numerous heavy metals such as, nickel, chromium, (Group 1 carcinogens) and cobalt (Group 2 carcinogen) according to IARC. These components are carcinogenic (cause cancer) and can contribute to the carcinogenicity of talcum powder products. Observational and experimental data confirm that talcum powder product particles applied to the perineum can reach the fallopian tubes and ovaries through the vagina, supporting that talc particles applied to the perineum can deposit on the ovaries. Surgery that impedes the movement of particles from the perineum to the ovaries such as hysterectomy (uterine removal) or tubal ligation (tying or blocking the fallopian tubes to the ovaries), reduces the elevated risk of ovarian cancer from exposure to talcum powder products. This finding supports that local tissue response and inflammation in the fallopian tubes and/or ovaries from talcum powder products (with components) causes the elevated ovarian cancer risk.

In summary, **from my review of the scientific literature and my own analysis, it is my opinion that genital exposure to talcum powder products is an actionable and causative risk factor for ovarian cancer.** As a physician involved in women's health issues, I view talcum powder usage as a modifiable "lifestyle" risk factor that should be avoided because of the substantial risk to health and lack of therapeutic benefit. An elevated risk of 50% is significant and results in a large number of unnecessary ovarian cancers given the large number of women exposed. Depending on estimates of how many women regularly use talcum powder products, between 7% and 20% of all ovarian cancers and 14% - 39% of invasive serous cancers (the most aggressive and feared cancer type) are caused by the use of talcum powder products. These cancers can be prevented if women do not use talcum powder products.

II. Qualifications

Education and Employment

I am a professor of Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Medicine, and Health Policy at the University of California San Francisco (UCSF) School of Medicine. I graduated from Princeton University with a degree in structural engineering (with combined majors in engineering and architecture) and attended UCSF medical school. My training after medical school included an internship, radiology residency, and clinical fellowship in women's health and a research fellowship in epidemiology and biostatistics in the UCSF Departments of Medicine and Epidemiology and Biostatistics.

I am a clinician-scientist. My clinical work includes one day a week in the Department of Radiology and Biomedical Imaging, with a focus on women's health imaging. I work in the ultrasound section, where a large proportion of the work is focused on the diagnosis of ovarian abnormalities (cancer and other functional issues). I run the UCSF Radiology Outcomes Research Lab, spending most of my time on clinical research and leading large epidemiological studies. I teach in the UCSF School of Medicine and Department of Epidemiology and Biostatistics.

Research Expertise

My research expertise is in epidemiology, outcomes research, comparative effectiveness, health services research, and dissemination and implementation sciences. My epidemiological studies have evaluated the quality, use, accuracy, predictive value, and impact of diagnostic testing on patient health. I have measured the risks and benefits of medical imaging in different contexts and different populations. Much of the research is in women's health, including diagnoses of cancers such as ovarian, endometrial, thyroid and breast. I have led many large, multi-institutional research projects. These projects are typically collaborative, involving researchers and clinicians with diverse expertise including radiology, obstetrics and gynecology, medicine, biostatistics, epidemiology, economics, demography, social sciences, medical informatics, radiation science, and dissemination and implementation science.

I have been a prolific researcher. I have led projects funded by more than 50 million dollars in research grants—entirely focused on cancer diagnosis and prediction. The research has been published in the most prestigious medical journals including the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Journal of the American Medical Association*, *Journal of the American Medical Association Internal Medicine*, *Journal of the National Cancer Institute*, *Obstetrics and Gynecology*, and leading radiology specialty journals such as *Radiology* and *Journal of the American College of Radiology*.

Knowledge of Relevant Study Designs

Several of my published studies have been systematic, meta-analytic, quantitative reviews of the published literature. Meta-analyses review existing evidence on a topic and summarize

and re-analyze data from earlier studies. My systematic reviews focused on the diagnoses of endometrial cancer, breast cancer, and a range of birth defects including trisomy 21 (Down syndrome) and trisomy 18 (Edwards Syndrome). Many of my reviews were published in prestigious medical journals, reflecting their scientific rigor based on an in-depth understanding of how to combine and review results from different studies in a scientifically valid and reproducible way.

Several of my recent research projects quantified the variation in radiation dose associated with medical imaging and the expected impact of this variation on cancer outcomes. This work has brought attention to the need for better standards in medical imaging. I am currently leading two large, multi-institutional epidemiological projects on medical radiation funded by the National Institutes of Health. One project is collecting radiation dose measures associated with computed tomography (CT) imaging from more than 150 hospitals in the United States, Europe, and Asia and testing the impact of providing feedback and education to radiologists on average and high doses. The second project is a multinational epidemiological study on childhood cancer. This project is assessing the risk of cancer associated with medical imaging among 1 million children and 1 million pregnant patients after accounting for a range of other cancer risk factors. The study will be the first to quantify the risk of medical imaging including CT among a large group of patients and uses novel methods to accurately estimate radiation dose from imaging.

I have expertise in a range of research study designs. The projects I currently lead (each funded by the National Institutes of Health or the Patient-Centered Outcomes Research Institute for between 9 - 15 million dollars each) have designs selected to be appropriate for the research question. For example, the study assessing the risk of cancer from medical imaging uses a *case-control study design*, *in which data are collected on a group of patients and those with a condition (cases), are matched to similar patients without the condition (controls)*. Matching people with a disease to people of similar age, gender, and other factors who do not have the disease allows researchers to determine if circumstances such as exposure to a potential toxin influence disease development.

My project on medical imaging uses a *cohort design*, *comparing groups of people (cohorts) in a population, some exposed to a potential disease agent and some not exposed*, to see if the agent influences disease. My study on radiation doses from CT uses a *randomized controlled design*, *in which individual patients are randomly assigned to different treatments* so their effectiveness can be compared. I am studying lung nodules using a *cluster-randomized controlled trial design that randomly assigns groups of people in similar circumstances (for example because they all see the same doctor) to different treatments* so the effects of the treatments can be compared.

I have a deep understanding of how epidemiological studies are conducted. I understand what study designs are suitable to particular datasets, populations, and research questions and the advantages and disadvantages of each design. This is relevant as no single study

design is "best;" there are strengths and weaknesses of each. The most appropriate and valid study design varies based on the research question being asked.

Experience as a Medical Expert

For the National Academy of Medicine, I have contributed to several reports, including Saving Women's Lives (2004), Improving Mammographic Quality Standards (2005), and Breast and the Environment: A Life Course Approach (2012), for which I wrote a review on the association between radiation exposure and breast cancer (Appendix). In addition to this research, I am actively involved in raising awareness of the need for better standards and greater safety around medical imaging, in particular related to radiation exposure. I have spoken at the US Food and Drug Administration, testified before the US Congress on several occasions, and worked with leading professional societies to focus attention on improving medical imaging safety. I have written several quality measures on radiation dose adopted by the National Quality Forum and developed educational tools to help physicians and patients understand the importance of minimizing radiation exposure from imaging.

Prior to providing my opinions on the association between talcum powder products and ovarian cancer, I had not reviewed the relevant literature and had not published in this area. As a result, I brought an unbiased perspective to my review. This report reflects my review of medical and scientific publications in this area (overviews and scientific studies), my own analysis, and review of documents shared with me by the lawyers who engaged me for this task. My curriculum vitae is attached as Exhibit A, the materials I considered are attached as Exhibit B, and my fees and prior testimony are attached as Exhibit C.

III. Background: Ovarian cancer and Talc as a Modifiable Risk Factor

Ovarian Cancer

Ovarian cancer is the seventh most common cancer in women and the fifth leading cause of cancer deaths in the United States. [1] In 2018, 22,240 women are expected to receive a new diagnosis of ovarian cancer and 14,070 women will die from it. Overall, about 1 in 78 women (1.3%) will be diagnosed with ovarian cancer in their lifetime and around 1 in 108 will die of it. About 224,940 women are currently living with ovarian cancer. [2] Most cases occur among older women; the median age at diagnosis is 62, although this varies by ovarian cancer type. [2]Ovarian cancer is frequently diagnosed at a late stage, when a cure is unlikely. Because so many ovarian cancers are diagnosed at a late stage, the overall mortality rate is high, and the overall 5-year survival is poor. With the poor prognosis and absence of a reliable screening test to find ovarian cancer early, it is a highly feared cancer for women and their physicians alike.

Histologic types

Cancers are classified by histologic type, meaning the type of cells that are involved. Understanding ovarian cancer histologic types is important because the risk factors, etiology and genetics of ovarian cancer can vary by histological type. Therefore, the importance of talcum powder products as a risk factor or cause can also vary by type.

Ovarian cancers (epithelial and non-epithelial) are a heterogeneous group of malignancies that vary in their pathological appearance, molecular biology, risk factors, etiology and prognosis. [1] Epithelial ovarian cancers have several histologic types; most fall into a small group of more common types including serous, endometrioid, clear cell and mucinous. About 90% of ovarian cancers are epithelial (meaning they arise from cells on the surface of the ovary or fallopian tube) and the most common type of epithelial cancer is serous carcinoma. Serous is not only the most common type of ovarian cancer, it is also the most lethal type of ovarian cancer. Further, it is the type of cancer that pathologists can most consistently, reliably, and reproducibly diagnose. Thus, epidemiological studies will have the greatest ability to document a clear association between serous ovarian cancer types and talcum powder products, if a connection exists. It is also the subtype that has been studied most from a molecular and pathologic research standpoint.

Table 1. Histologic Types of Ovarian Cancers Diagnosed Over 15 Years at the KP Washington (in press, JAMA Internal Medicine)

Histologic Type	Number	Percent of Total Cancers
Papillary serous cystadenocarcinoma	52	36.6
Endometrioid carcinoma	17	12.0
Serous cystadenocarcinoma	15	10.6
Clear cell adenocarcinoma	12	8.5
Adenocarcinoma, NOS	11	7.7
Mucinous adenocarcinoma	7	4.9
Mixed cell adenocarcinoma	3	2.1
Serous surface papillary carcinoma	3	2.1
Granulosa cell tumor	3	2.1
Carcinoma, not otherwise specific	2	1.4
Mucinous cystadenocarcinoma	2	1.4
Mucinous cystic tumor of borderline	2	1.4
Carcinoma in situ	1	0.7
Squamous cell carcinoma	1	0.7
Papillary adenocarcinoma	1	0.7
Papillary serous cystadenoma, borderline	1	0.7
Adenocarcinoma with squamous meta	1	0.7
Granulosa cell tumor, malignant	1	0.7
Endometrial stroma sarcoma	1	0.7
Mullerian mixed tumor	1	0.7
Carcinosarcoma	1	0.7
Carcinosarcoma, embryonal	1	0.7
Teratoma, malignant	1	0.7
Astrocytoma	1	0.7
Marginal zone B-cell lymphoma	1	0.7
Total	**142**	**100**
Summary		
Serous carcinoma	70	49.3
Endometroid carcinoma	17	12.0
Clear cell carcinoma	12	8.5
Mucinous carcinoma	9	6.3

My research group recently reported on the ultrasound appearance of ovarian cancers among a large cohort of women. The purpose of this cohort study was to quantify the risk of malignant ovarian cancer based on ultrasound findings. We described 142 new ovarian cancer cases in a population of 500,000 women enrolled in Kaiser Permanente Washington, an integrated health plan, between 1997 and 2008, including 72,093 women who underwent pelvic ultrasound. The distribution of cancer histological types is in Table 1. Serous carcinoma was the most common cancer type: In our cohort, it was 50% of the ovarian cancers. Serous carcinoma has the worst prognosis of the ovarian cancer types. Its high frequency and poor

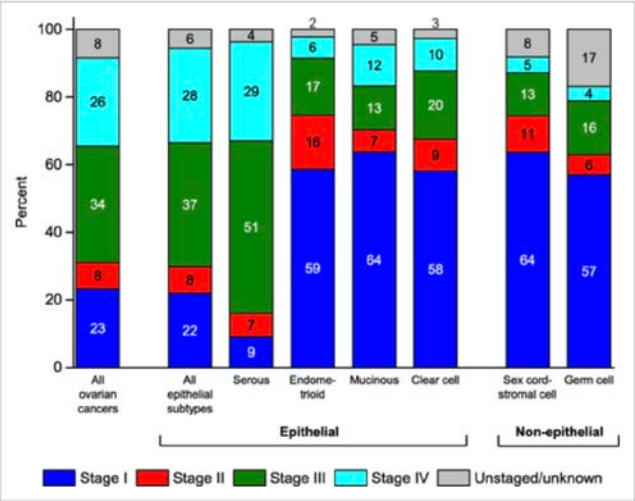
prognosis contribute to the high mortality rate for ovarian cancer overall. The other common histological types of ovarian cancer were endometrioid (12% in our data), clear cell (8.5% in our data), and mucinous (6.3% in our data).

Ovarian cancer types have large differences in stage of diagnosis (a strong predictor of survival) and prognosis independent of stage. The 5-year survival by histological type is in Table 2. Serous cancer is the most frequent and most aggressive, with an overall 5-year survival of 43% as compared with 82% for endometrioid. The survival is strongly influenced by stage at diagnosis, with higher stage numbers indicating more advanced stage. [1] Most serous carcinomas are diagnosed at stage III (51%) or IV (29%) (Figure 1), [2] for which 5-year survivals from the most recent data were 42% and 26%, respectively. These data reflect the aggressive nature of serous cancer. [1] In contrast, the majority (58% to 64%) of endometrioid, mucinous, and clear cell carcinomas are diagnosed at stage I, similar to nonepithelial tumors (Figure 1) . Consequently, the 5-year survivals are 82%, 71%, and 66%, respectively, for endometrioid, mucinous, and clear cell carcinoma. Thus, these cancers behave very differently, even though all are ovarian epithelial cancers.

Table 2. Percent of Women Surviving 5 Years After Diagnosis by Epithelial Ovarian Cancer Type. Data From 2008–2013.

	All epithelial types	Serous	Endometrioid	Mucinous	Clear cell	Sex cord-stromal	Germ cell
Stage							
All	47	43	82	71	66	88	94
Stage I	89	86	95	92	85	98	99
Stage II	71	71	84	69	71	84	93
Stage III	41	42	59	30	35	61	90
Stage IV	20	26	29	13	16	41	69

Figure 1. American Joint Committee on Cancer Sixth Edition Stage Distribution (%) for Ovarian Cancer by Histology, US, 2007-2013, SEER 18 Registries, NCI, 2017. This shows that serious cancers are more likely to be diagnosed at state III, IV (green and teal), compared with other tumor types.



This summary reflects our current knowledge about ovarian cancer histologic types and their associated prognoses. As research results are reported, our knowledge will evolve. For example, recent studies suggest we need to improve our ability to distinguish between high-grade serous and endometrioid carcinomas. Other results suggest that many ovarian mucinous carcinomas are actually gastrointestinal tumors that metastasized to the ovaries and this realization is affecting the reported rates of ovarian mucinous carcinomas (which are declining). [1,3,4] The categorization of noninvasive tumors classified as borderline is also under investigation and a topic of discussion in the field. These noninvasive tumors have historically been considered in the spectrum of ovarian cancer that have less aggressive behavior. However, many previously described borderline cancers are now generally considered non-malignant.

In summary, when assessing the carcinogenicity of talcum power products, this should focus on invasive serous carcinoma as the most important cancer (based on prognosis) and the most reliable cancer to identify (based on histology and understanding of cancer behavior).

Additionally, over the last decade, there has been research suggesting that many ovarian cancers originate from cells in the distal portion of the fallopian tube. Because the pathogenesis, treatment, and prognosis of serous cancers of the fallopian tube, ovary, and peritoneum are similar, these are now typically considered as a single entity. [4] This consideration applies to the association with talcum powder product usage discussed in this report.

Risk Factors

Understanding ovarian cancer risk factors is important because analyzing the impact of talcum powder products exposure must consider *covariates, or other characteristics* that a woman might have that might also influence her ovarian cancer risk such as age, inherited genetic mutations, reproductive factors, or family history of cancer. Every risk factor does not have be considered to come to a valid conclusion; indeed, this is not realistic within the limitations of medical research, and the bias introduced by the exclusion or some risk factors will be small. However, crude analyses that look at the risk of ovarian cancer from talcum powder products without adjusting for any other risk factors must be considered cautiously. For that reason, statistical analyses of research results often adjust for *confounding factors or variables that are covariates that hinder accurate calculation of an association,* for example between talcum powder products and ovarian cancer.

Numerous risk factors are identified for ovarian cancer. [5] Unfortunately, few can be modified by therapies or lifestyle changes. Risk factors vary by histologic type [5] but those that increase risk of ovarian cancer include personal or family history of ovarian or breast cancer, inherited mutations including BRCA1 and BRCA2 [6-10] advanced age, white race, increased education, and endometriosis. Other factors that may increase ovarian cancer risk due to estrogen exposure include having no pregnancies or advanced age at first birth, obesity, and postmenopausal hormone therapy. [11-13] Several factors are associated with reduced risk for ovarian cancer including breast feeding, multiple pregnancies, use of oral contraception,

tubal ligation, and removal of uterus, fallopian tubes, or both. [14-18] Smoking is a possible risk factor for ovarian cancer, primarily mucinous subtype, although study results have not been consistent. [5,19]

Risk factors vary by cancer type. For example, serous cancer is more strongly associated with reproductive risk factors than mucinous tumors [20-22] and different histologic types have different molecular and genetic profiles. [23-25] Serous tumors are more likely to have a cancer-promoting mutation in the p53 gene, whereas similar KRAS mutations are more common in mucinous tumors. Over time, the occurrence of ovarian cancer has changed, in part due to changes in risk factors. For example, small declines in the rates of endometrioid and serous cancer are attributed to declining use of hormone replacement among postmenopausal women.

Etiology: Origins, Causes, Development and Inflammation

Our understanding of the etiology and course of ovarian cancer continues to evolve. Hereditary genetic predisposition increases risk, but overall, accounts for only a small proportion of cancers. And even in women with hereditary genetic mutations, not all will develop ovarian cancer. The majority of ovarian cancers are now believed to arise in the distal portion of the fallopian tube. By convention, fallopian tube, ovary and peritoneal cancers are considered as a single entity. The most widely accepted mechanism for initiation, promotion and progression of ovarian cancer is tissue inflammation leading to a series of responses that result in cancer.

There is very clear and extensive scientific literature describing the relationship between inflammation and cancer across many anatomic areas. Chronic inflammation, and even subtle, subclinical inflammation, is associated with an increased risk of cancer. [26-28] Many inflammatory conditions predispose to cancer development. Diverse factors that lead to inflammation - infection, chemical exposures, physical agents, autoimmune factors, and even inflammatory reactions of uncertain etiology - can lead to an increase in cancer incidence. For example, there are well described and accepted causal pathways linking inflammation in the etiology of bladder cancer (schistosomiasis, toxic chemicals), cervical cancer (papillomavirus), gastric cancer (H Pylori), colon cancer (inflammatory bowel disease), liver cancer (hepatitis), mesothelioma (asbestos) and ovarian cancer (pelvic inflammatory disease and endometriosis). The biological pathways associated with inflammation include stimulation/interference with a range of biological responses that are involved in initiation of cancer, promotion of cancer, and progression of cancer. Oxidative stress resulting from inflammation can impact all stages of cancer development including cancer initiation (DNA is damaged by introducing gene mutations and structural alterations of DNA leading to inhibition of DNA repair and malignant transformation); promotion (which may be manifest as abnormal gene expression resulting in cell proliferation and decrease apoptosis) and progression (further DNA damage and enhancement of cell growth. [29] Local inflammatory response can lead to signaling molecules such as cytokines, chemokines, prostaglandins, growth transcription factors, microRNAs having higher expression that can promote cancer

development and can create a favorable microenvironment for the development and progression of cancer. [30] Inflammation impacts every step of tumorigenesis, from initiation through tumor promotion, and extending to metastatic progression. Similarly, the most compelling mechanism for the etiology of ovarian cancer is that of chronic inflammation and scarring in the ovary that leads to malignant transformation and cancer progression. This mechanism involves cell proliferation, oxidative stress, DNA damage and gene mutations. [31-33] [31,34-37] The microenvironment of ovarian cancer contains a broad spectrum of pro-inflammatory cytokines and chemokines contributing to the mechanism. [38]

There are many processes that can lead to inflammation and tumorigenesis and the exposure to talcum powder products is one such exposure that can strongly enhance the tumor promotion or progression as seen in in vitro and animal studies. For example, normal repeated ovulation leads to injury of ovarian epithelial cells and transformation to malignant cancer cells that can be enhanced by various factors such as talc or asbestos particles. Exposure to talcum powder products can induce the production of pro-oxidant enzymes and reduced production of antioxidant enzymes leads to malignant transformation. In support of inflammation from talcum powder products causing cancer, hysterectomy or bilateral tubal ligation, which would significantly limit ovarian exposure to inflammatory mediators, and toxins, is associated with reduced ovarian cancer risk.

Relationship Between Ovarian Cancer and Talcum Powder Products

The epidemiological evidence described in detail below demonstrates a strong and positive association between exposure to talcum powder products and ovarian cancer and that talcum powder products cause ovarian cancer. Although epidemiologic evidence alone does not provide a definitive mechanism or pathophysiological process that accounts for the increased risk, the evidence for inflammation as described above is very strong. Similarly, epidemiological evidence alone does not confirm the specific component or ingredient in talcum powder products that is responsible for its carcinogenesis. Nonetheless, several constituents within talc powder products are worth highlighting as they may be acting individually or together to create the carcinogenicity of talc powder products inasmuch as they are individually highly carcinogenic

Why Talcum Powder Products were Initially Suspected as Causing Ovarian Cancer

In 1978 samples of commercial body powders were shown to contain asbestos silica minerals. Asbestos was a known carcinogen and about half of the powder samples contained respirable quartz, a lung carcinogen. Concerns were primarily raised that inhaled powder could cause lung scarring, lung cancer, or mesothelioma. In 1971, Henderson observed talc particles deeply embedded in ovarian cancer tissue. The authors noted the close association of talc to the asbestos group of minerals. [39]Further concern was raised , in 1982 whena case-control study of ovarian cancer that collected information on talcum powder use reported an increased risk with perineal dusting. [40] These findings were reported in widely circulated newspapers such as The Globe, raising concern that the powders were carcinogenic because

of the contamination with asbestos, using the relationship between asbestos and lung cancer and mesothelioma as the basis for the concern.

Carcinomic of Constituents of Talc Powder Products

There are hundreds of different constituents and ingredients within talcum powder products in addition to platy talc. Many of these are Group 1 carcinogens (such as asbestos, talc containing asbestiform fibers, heavy metals, and some fragrance chemicals) that likely contribute to the carcinogenicity of the products.

Asbestos

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibers; serpentine mineral fibers are called chrysotile, and amphibole minerals include actinolite, amosite, anthophyllite, crocidolite and tremolites. Talc is formed by complex geological processes acting on pre-existing rock formations with diverse chemical composition. Small amounts of chrysotile (asbestos) may occur in these talc deposits [41,42] When talc is mined it may contain asbestos fibers [42,43] A study of 21 consumer talcum powders obtained from retail stores in 1971–1975 reported that 10 contained concentrations of asbestos fibers ranging from 0.2 to 14%. [41,44] Because of concern that asbestos was present in talcum powder products and the known carcinogenicity of asbestos, it has been reported that voluntary guidelines were established by the cosmetic industry in 1976 to limit the content of asbestos fibers in commercial talc preparations. While currently talcum powder products are believed to free from asbestos, the data on its continued presences are strong. I have seen evidence of continued presence since 1976. [45-48] For example, Longo tested approximately 50 samples that were taken between the years 1960 through 2000 and the majority of sample are positive for asbestos. [47]

Asbestos is a known and potent human carcinogen. Asbestos is highly carcinogenic to the lungs, lining of the lungs, and larynx. [49] Asbestos is also highly carcinogenic to the ovaries. [49-58] Women working in asbestos-manufacturing industries have an increased risk of ovarian cancer. IARC reviewed the association between asbestos exposure and ovarian cancer in 2012. To assess the relationship, IARC reviewed data primarily from large epidemiological cohort studies of women who had occupational exposure to asbestos as well case-control studies on non-occupational exposure. The context and lengths of exposures varied, along with the type of asbestos fibers to which the women were exposed and the study designs and assessments. Nonetheless, the results were consistent. Most, but not all, were statistically significant and documented a strong and compelling causal association between exposure to asbestos and ovarian cancer, largely the result of the association from cohort studies of women with substantial occupational exposures. [50-54] **IARC concluded that there is sufficient evidence that asbestos is carcinogenic in humans and that asbestos causes cancer of the ovary**.This is the highest risk category. [49] IARC also concluded that this categorization applied to all forms of asbestos and to talc containing asbestiform fibers (talc in a fibrous habit or fibrous talc)). IARC also concluded that asbestos is carcinogenic based on animal studies. Camargo completed a systematic review of the relationship between women occupationally exposed to asbestos and ovarian cancer. [59] The authors found that of the 18 cohort studies

the pooled standard mortality estimate for ovarian cancer was 1.77 (95% confidence interval, 1.37-2.28). The range in reported SMR values was 1.1– 5.4 across the included cohort studies and the most common values were 2–3. This study supports IARC's conclusion that exposure to asbestos causes ovarian cancer.

IARC explicitly stated that the findings in this Monograph applied to all forms of asbestos, as well as asbestiform talc (fibrous talc).

I reviewed many publications and primary research studies, including experimental and basic science models showing molecular and genetic cancer-promoting changes to cells that occur from exposure to asbestos fibers. I also strongly conclude that asbestos causes ovarian cancer.

Talc

Talc is the primary component of talcum powder products. The chemical structures of talc and asbestos can be similar. While talc particles are usually plate-like, talc can also grow as a fiber which is similar to the group of minerals called asbestos. Both are magnesium silicate and when talc has the fibrous form it is called asbestiform because of its similarity to asbestos. The form of the talc fibers is long and thin, with parallel bundles that are easy to separate from each other, and closely resembles the physical appearance of asbestos minerals. The histologic appearances of mesothelioma and ovarian cancer are similar. The known carcinogenicity of asbestos for lung, pleural, peritoneal and ovarian cancer has led to the theory that the similarity in the fibers and the resulting cancers suggests that talc works mechanistically within the ovary to induce cancer in a way that is similar to how asbestos in the chest induces mesothelioma.

Early observations demonstrated talc particles in both malignant and normal ovaries establishing a route from the perineum to the ovary and shows that many women are exposed to talc. [39,60] In 2006, the International Agency for Research on Cancer (IARC) reviewed the data on cosmetic (perineal) talc ("non-asbestiform") application and concluded that it is possibly carcinogenic to humans. [61] This is not as strong a recommendation as they made for asbestos and ovarian cancer, but nonetheless is a strong recommendation. IARC classified genital-perineal use of talc-based powder as possibly carcinogenic. Exposure to talc particles can induce an inflammatory response, either directly at the ovary and ovary-fallopian tube juncture, causing local irritation from talc particulates or through more generalized peritoneal inflammation. The mechanism that can lead to cancer is local irritation by talc fibers that disrupts the epithelial surface, increasing rates of cell division and DNA repair that can lead to mutations. Also increased are oxidative stress and cytokine production, indicating inflammation. Fibers that are incorporated into the epithelial cells enter ovarian tissue. This inflammation initiates a series of responses, supported by research, that promote cancer. The reduction in the elevated risk of ovarian cancer from talcum powder exposure after hysterectomy or tubal ligation supports the mechanism by which local irritation and inflammation to the ovary from talc or asbestos causes an elevated cancer risk.

Heavy Metals

Talc powder products can contain Group 1 metals that are considered by IARC as carcinogenic to humans. [44,49] This includes nickel compounds which IARC documents cause lung and nasal cavity and paranasal sinus cancer. (IARC100c-10, 2012). Nickel compounds "cause DNA damage, chromosomal aberrations, delayed mutagenicity and chromosomal instability … and nickel compounds act as co-mutagens." Talcum powder products also contain Chromium (VI) (IARC100c-9, 2012) another Group 1 carcinogen, where there is sufficient evidence in humans for carcinogenicity (to the nose and nasal sinus). The mechanism includes "DNA damage, generation of oxidative stress and aneuploidy. Talc powder products can also contain Group 2A metals that are considered probably carcinogenic to humans, such as Cobalt which can be found in talc powder products. [62] IARC considers Cobalt metal with tungsten carbide as probably carcinogenic to humans (Group 2A), but worth noting that a number of the IARC working group members supported an evaluation in Group 1 because they judged the epidemiological evidence to be sufficient, leading to an overall evaluation in Group 1; or they judged the mechanistic evidence to be strong enough to justify upgrading the default evaluation from 2A to 1. The majority of working group members, who supported the group 2A evaluation, cited the need for either sufficient evidence in humans or strong mechanistic evidence in exposed humans. Cobalt metal without tungsten carbide is also considered possibly carcinogenic to humans (Group 2B). Cobalt sulfate and other soluble cobalt(II) salts are possibly carcinogenic to humans (Group 2B).

Any and all of these heavy metals can cause ovarian cancer through an inflammatory mechanism

Fragrances

There are more than 150 different chemicals added to Johnson's Baby Powder and Shower to Shower products. I reviewed the expert report from Dr. Crowley that concludes that some of these chemicals may contribute to the inflammatory response, toxicity, and potential carcinogenicity of Johnson & Johnson's talcum powder products. I concur with his opinion. [63]

IV. Overview of Publications on Genital Use of Talc Powder Products and Ovarian Cancer

To understand the relationship between exposure to talcum powder products and ovarian cancer, I searched for and reviewed scientific papers on this topic. I used several searchable publication databases (Scopus, Embase, Pubmed) and manually searched the reference lists of all articles I found, including a large number of reviews. The results of my review follow the explanation of the main types of studies and articles.

Explanation of study designs and article types

Nearly all published studies that I reviewed used one of two designs: case-control and cohort. Each design has strengths and biases. The commonly held view is that cohort studies are better than case-control studies. This is a misconception thus it is worth explaining their differences. Many articles I reviewed were systematic reviews, which are also explained.

Case-control studies compare people with a condition (cases) by matching them to people with similar characteristics who do not have the condition (controls) to determine the effect of a potential disease-causing factor. They often analyze existing data *retrospectively, after people have been diagnosed,* and involve tens or hundreds of patients. *Cohort studies compare cohorts, or groups of people, who were exposed or not exposed to a potential disease agent.* They often collect data on people *prospectively, before they develop a disease* and track their health over time. Both case-control and cohort studies, if well done, can provide accurate and meaningful information about statistical associations. In general, however, the risk of bias is greater for case-control studies. (An example is *recall bias*, in which women are more likely to remember and report exposure to talc powder products after they have been diagnosed with cancer compared to women without a diagnosis, perhaps because diagnosed women heard that talc powder products is harmful and are more likely to remember talc use). Nonetheless, when studying a rare disease, the case-control design is frequently highly efficient and desirable as it allows you to assemble a much larger number of cases and can delve in great depth for particular exposures. You can identify all patients who have the outcome of interest, and then query them (and some control group) about any antecedent exposure. The identification of the control group is very important. My large, National Institutes of Health-funded study of cancer risk factors in children is employing a case-control design. This design permits us to ask very detailed questions of a small number of individuals about their various exposures.

Cohort studies potentially avoid some biases of case-control studies since exposures are prospectively assessed and quantified, that is, before disease outcomes. This design also has limitations, though. An extremely important limitation is that because cohort studies are expensive and time-consuming, they rarely focus on a single, narrowly defined question such as the association between regular use of talcum powder products and cancer. Usually, researchers investigate a broad range of questions in cohort studies, so asking patients in-depth questions about any given topic is difficult, especially since tens of thousands of patients may be surveyed on many topics. Further, in cohort studies, having comprehensive assessment of outcomes on all individuals in the cohort is extremely important. Losing patients to follow up (meaning researchers cannot contact or find records on a participant) leads to study bias. The other disadvantage of cohort studies is that a very large number of patients must be assessed over a long period of time to see who will develop a rare outcome (like ovarian cancer). Because of this, typically there will be far fewer patients with disease in a cohort study as compared with case control study (like in this case).

The small number of cohort studies I found on the relationship between talcum powder products exposure and ovarian cancer did not focus on the details of this topic. While they may have included questions about talcum powder exposure, they were not sufficiently nuanced to provide meaningful information. Thus, in most of the cohort studies I found, measurements of exposure were poor, not specific, or inaccurate. Further, several had very short follow-up periods with data or information about the time before the cancer occurred. This negates an advantage of cohort studies, which is being able to learn about exposures before the cancer, eliminating recall bias.

Systematic reviews quantitatively summarize results across multiple studies. One of the rationales of this study design is that individual studies may not have enough participants to yield meaningful results because they are too small or insufficiently powered. Combining small studies can provide more stable and reliable summary estimates of the effects of disease agents and risk factors. Further, a systematic review may be better than a single study, as it provides broader evidence of the results and includes patients from diverse settings. However, in order to statistically combine and summarize the data from different research studies into a single systematic meta-analytic review, the combined studies must ask the same research question and follow sufficiently similar and rigorous scientific methods. A meta-analysis does not compensate for gaps or flaws in an original study: Combining three poorly performed studies does not yield reliable summary estimates even though there may be three times the number of patients. Similarly, combining studies that ask different research questions (for example, assessing women of different ages for a disease in which age is an important risk factor) does not provide reliable summaries. Results from different studies often vary when the studies ask different research questions, have different criteria for including participants, or use different methods. I raise these issues to point out that systematic reviews must be read extremely carefully to ensure that their conclusions are valid.

Table of Reviewed Publications

I identified and reviewed 43 English-language publications that provided quantitative data based on epidemiological studies about the relationship between genital talcum powder exposure and ovarian cancer (Table 3). This list includes 4 cohort studies, 8 systematic meta-analytic reviews, 2 studies that pooled individual patient-level data from several research studies, and 30 case-control studies. One study contributed both the systematic review and a case control study. I also read multiple review articles that are not included in the table. The epidemiological studies were published between 1982 and 2018. I have described the results organized by study design below.

Most studies used a case-control study design with a small number using a cohort study design. Although some studies assessed powder use to any part of the body or assessed the use of talcum powder on diaphragms, condoms or sanitary napkins, the primary research question that I focused on in my review and that was assessed in all included individual research studies, was whether genital area exposure to talcum powder increases risk of epithelial ovarian cancer. Occasionally, study authors assessed combination exposures (i.e., to genitals and other body parts). These studies were included as long as genital powder use was assessed. Nearly all studies adjusted for known ovarian cancer risk factors, but those factors varied. The vast majority of studies found a positive association between any exposure to talcum powder products and cancer. However, the sample size of some studies was small and resulted in high statistical uncertainty. Because of these and other limitations, quantifying a precise association between exposure and cancer was difficult from my review of the literature. The data for some studies may have shown that effects of talcum powder exposure (measured as odds ratios, ORs) was meaningful for cancer development, but with statistical

uncertainty; whereas other studies showed the reverse results, with ORs not showing a positive association, but statistical parameters suggesting that a meaningful association was nonetheless possible because of wide confidence intervals. Therefore, I thought a more precise and careful review was called for. The number of individual women included in each study and the reported or estimated effect size for "any exposure to talc" (adjusted for other risk factors such as age) are in Table 4.

A subset of the studies quantified the *intensity (frequency)* of each woman's exposure to talc to assess the importance of use patterns (e.g., if a single lifetime use or weekly, monthly, or daily use increased ovarian cancer risk) or *dose dependency (links between the number of exposures and cancer risk, e.g., if doubling exposure doubles risk)*. Further, a subset of studies stratified by cancer type (invasive vs. low malignant potential/borderline) and whether the risks varied by histological types including the four dominant types of serous, mucinous, clear cell, and endometrioid cancer.

Studies that provided data on the frequency of talc use and association by histologic type were included in a separate systematic meta-analytic review that I conducted as part of my review of the literature to include in this report. The reason I completed my own statistical review is further explained below.

Quantifying Exposures

A large proportion of women will have used talcum powder products, highlighting the importance of this issue. However, publications that focus on women reporting "any" genital exposure to talc (i.e., talc at any point in life and for any duration) may be too broad to provide meaningful information. For example, "any use" will include women who applied talc powder products three times over five decades and women who used talc powder products daily, whose might have had 20,000 applications and exposures in comparison to three. Defining a variable as any use is the equivalent to creating a variable of any smoking use, that combines data on individuals who tried one cigarette in their life with individuals with 50 pack years of tobacco use. Combining data on women with infrequent or sporadic exposures with data from women with frequent, sustained use leads to imprecise results, masking any causal associations. Therefore, I selected the studies for my own review that quantified the frequency of talc powder products use as having the most informative data and included them in a separate systematic review.

Summary of Data

I grouped the research studies by their study design. What follows is my review of the cohort studies, systematic review studies, pooled data studies, followed by my own review.

Cohort Studies

Four cohorts (Gertig, Gates, Houghton, Gonzalez) have been published on talcum powder products and ovarian cancer.

Cohort 1: Gertig (2000) [64]

This first cohort study assessed the relationship between perineal talc and ovarian cancer within the context of the US Nurses' Health Study, a prospective study of 121,700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. These are mostly premenopausal women. While talc exposure was not an initial part of the study, questions about talc, including measuring frequency of exposure, were added in 1982; a large subset of the cohort (78,630 women) completed these questions and were included in analyses. Among these women who were followed for 14 years, 307 were diagnosed with epithelial ovarian cancer. After adjusting for confounding variables, the *relative risk (RR)* of developing ovarian cancer (*the likelihood of ovarian cancer in talc users compared to nonusers, with higher RR meaning increased risk stronger association*) among daily users of talc was RR 1.12 (95% *confidence interval [CI]* 0.82, 1.55, *a measure of statistical uncertainty, with wider ranges indicating greater uncertainty*), which was not statistically significant. However, when results were classified by histologic subtype, the RR of invasive serous cancers was significantly elevated among any users of talc (RR 1.40, 95% CI 1.02, 1.9) and the RR of invasive serous cancer among daily users of talc was higher at RR 1.49 (95% CI 0.98, 2.3).

In this cohort study, the researchers assessed talc exposure before cancer diagnosis, avoiding the possibility of the recall bias of case-control studies. This was a strong strength of this study. A potential weakness was that frequency (i.e. daily) but not duration (number of years) of talc use was measured, so a clear lifetime exposure measure was missing. The researchers nonetheless quantified exposure at the time the talc questions were asked, which was probably strongly associated with prior use (i.e. an approximation on ongoing use). **This study provides strong evidence that perineal exposure to talc increases the risk of invasive serous ovarian cancer, particularly among daily users of talc, with about a 50% increased risk**, which is substantial and meaningful.

Cohort 2: Gates (2010) [24]

This study assessed the association between ovarian cancer risk factors and incidence of ovarian tumors by histological type using data from the US Nurses' Health Study combined with data from the Nurses' Health Study II, which included a second period of enrolling participants. Unfortunately, talc use was assessed only on the first survey and not assessed among patients enrolled in the Nurses' Health Study II. Thus, this extends the period of follow up from the initial NHS but does not include greater information about risk factors. Results were presented for any talc powder products use and not for frequency of use. **Thus, this report does not add to a meaningful assessment of the relationship between talc use and ovarian cancer because it used exactly the same patient group as Gertig (2000) but provided less information to quantify the frequency of talc use.**

Cohort 3: Houghton (2013) [65]

This study assessed perineal talc powder products use and risk of ovarian cancer in the Women's Health Initiative Observational study, in which postmenopausal women aged 50–79 were enrolled in a prospective cohort of women from 40 clinical centers across the United

States in 1993–1998. Overall, 61,576 women were included in analyses, including 429 diagnosed with ovarian cancer. Perineal powder use was assessed at the start of the study. Participants were asked if they **ever used talc powder products** on their private parts (genital areas). Those who responded yes were asked about duration (years) of use. Women were followed for a mean of 12 years and the median age of participants was 63. **Talc powder products use was associated with a 12% increase in risk of ovarian cancer after accounting for covariates** (RR 1.12, 95% CI 0.92, 1.36). When limited to women who used perineal powder for 20 years or more, the RR was 1.10 (95% CI 0.82, 1.48). When limited to serous ovarian cancer, the RR was 1.13 (95% CI 0.84, 1.51.) **The primary limitation of the study was that frequency of talc powder products use was not assessed—and thus the authors could focus only on any talcum powder use.** The imprecision in estimation of talcum powder exposure makes the results not terribly meaningful. The second limitation was the relatively short follow-up of 12 years to identify ovarian cancer diagnoses.

Cohort 4: Gonzalez (2016) [66]

The Sister Study (2003–2009) followed 50,884 women ages 35 to 75 years in the US and Puerto Rico who had a sister diagnosed with breast cancer. After excluding participants who had bilateral oophorectomies, ovarian cancer, or were lost to follow-up, 41,654 participants were included. At baseline participants were asked about douching and talc use during the previous 12 months, and during follow-up (median of 6.6 years) 154 participants reported a diagnosis of ovarian cancer. The authors computed adjusted hazard ratios (HR) and 95% confidence intervals (CI) for ovarian cancer risk using the Cox proportional hazards model. The authors found no significant association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73 CI: 0.44, 1.2). **The primary limitations of this study are that the authors combined a large number of potential talc exposures into a single category, including genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Further, the authors categorized the exposure based on the 12 months prior to enrollment as a dichotomous ever/never.** Thus not only was it an ever versus never category, the ever category was extremely broad, making the lack of association less meaningful. Further, there are several other factors that make the results questionable, including lower than expected proportion of women who report any exposure to talc powder products, and the lack of a validated approach to ascertainment of ovarian cancer.

Cohort Studies: Summary

Analyses of data from the US Nurses' Health study and the Women's Health Initiative estimated that women who report any exposure talc powder products will have a 12% increase in ovarian cancer compared to women who never report talc powder products use, although this estimate was not statistically significant. The primary limitation of this estimate is that it is based on *any talc powder products* use, which is a weak, crude predictor. Similarly, while the results from the Sisters study did not identify a significant association between talc powder products use and ovarian cancer, they too used a measure of ever use, and included a large number of different types of exposures that would not be expected to measure a single exposure. The most important and meaningful conclusion that I draw from the cohort studies

is from the Gertig 2000 study using data from the US Nurses' Health study: That women who are **daily users of talc have an approximately 50% increase (OR 1.49) in their risk of invasive serous** cancer, the most lethal and frequent type of ovarian cancer.

Systematic Reviews

I found nine systematic reviews that summarized the relationship between talc and ovarian cancer, summarized below. These reviews were completed using various subsets of the full list of publications. The systematic reviewers are presented with the most recent first, because the more recent studies tended to be more complete, comprehensive and the most methodologically rigorous.

Systematic Review 1: Penninkilampi (2018) [67]

This comprehensive systematic review of the association between any genital use of talcum powder products and ovarian cancer conducted a stratified analyses showing the association by frequency of talc use and histologic cancer subtype. The methods of the study are well described. The researchers identified studies using six electronic databases and reviewed publications with 50 or more cases of ovarian cancer. They identified 24 case-control studies describing 13,421 cases and the three cohort studies (890 cases, 181,860 person-years) described above. Any reported use of perineal talc powder products was associated with increased risk of ovarian cancer compared to no use (OR = 1.31; 95% CI 1.24, 1.39). Women with more than 3600 lifetime applications had slightly higher risks (OR = 1.42; 95% CI 1.25, 1.61). Women who reported long-term (>10 years) talc use also had an increased risk (OR 1.25; 95% CI = 1.10, 1.43). The association between any talcum powder product exposure and ovarian cancer was limited to studies that used a case-control design. The cohort studies showed an increased risk of serous invasive cancer subtypes for perineal talc use compared to no use (OR = 1.25; 95% CI = 1.01, 1.55). While serous and endometrioid cancer were associated with talcum powder products use, no association was seen with mucinous or clear cell cancers. The review authors concluded, from the data, that perineal talcum powder use and ovarian cancer were consistently associated, with a slightly higher risk in women who report greater usage. Some variation in the magnitude of the effect of talcum powder products was found when considering the study designs and ovarian cancer subtypes. Several small methodological issues are that Penniniklampi may have included some groups of patients more than once in analyses and did not include updated data or previously unpublished data available from a research consortium on ovarian cancer. However, these concerns are unlikely to have had a significant impact on their estimates.

Table 3. List of Included Studies, sorted by study design

	Study Type	Year	Author	Journal	Title
1	Cohort Study	2000	Gerting	J Natl Cancer Inst	Prospective study of talc use and ovarian cancer (in the Nurses' Health Study)
2	Cohort Study	2010	Gates	Am J Epidemiol	Risk factors for epithelial ovarian cancer by histologic type; US Nurses Health Study
3	Cohort Study	2014	Houghton	J Natl Cancer Inst	Perineal powder use and risk of ovarian cancer: Results from the Women's Health Initiativ
4	Cohort Study	2016	Gonzalez	Epidemiology	Douching, talc use and risk of ovarian cancer: Results from the Sister Study
5	Systematic Rev.	1992	Harlow	Obst Gyn	Perineal exposure to talc and ovarian cancer risk
6	Systematic Rev.	1995	Gross	J Expo Anal Env Epid	A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer
7	Systematic Rev.	2003	Huncharek	Anticancer Res	Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies
8	Systematic Rev.	2007	Huncharek	Eur J Cancer Prev	Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies.
9	Systematic Rev.	2008	Langseth	J Epid Community Health	Perineal use of talc and risk of ovarian cancer.
10	Systematic Rev.	2010	IARC	IARC Monographs	IARC monographs on the evalatuion of carcinogentic risks to humans: Carbon black, titanium dioxide, and talc
11	Systematic Rev.	2017	Berg	European J of Can Prev	Genital use of talc and risk of ovarian cancer: A meta-analysis
12	Systematic Rev.	2018	Penninkilampi	Epidemiology	Perineal talc use and ovarian cancer: A systematic review and meta-analysis.
13	Pooled Data	2013	Terry	Cancer Prev Res	Genital powder use and risk of ovarian cancer: a pooled analysis of 8525 cases and 9859 controls
14	Pooled Data	2016	Cramer	Epidemiology	The association between talc use and ovarian cancer- A retrospective case- control study two US states
15	Case-Control	1982	Cramer	Cancer	Ovarian cancer and talc: A case control study
16	Case-Control	1983	Hartge	JAMA	Talc and ovarian cancer
17	Case-Control	1988	Whittemoore	Am J Epidemiol	Personal and environmental characteristics related to epithelial ovarian cancer. Exposure to talcum powder, tobacco, alcohol, and coffee
5	Case-Control	1989	Harlow	Am J Epidemiol	A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc
18	Case-Control	1989	Booth	BR Cancer	Risk factors for ovarian cancer: a case-control study
19	Case-Control	1992	Harlow	Obstet Gynecol	Perineal exposure to talc and ovarian cancer risk
20	Case-Control	1992	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer
21	Case-Control	1992	Chen	Int J Epidemiol	Risk factors for epithelial ovarian cancer in Beijing, China
22	Case-Control	1993	Tzonous	Int J Cancer	Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer
23	Case-Control	1995	Purdie	Int J Cancer	Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study
24	Case-Control	1996	Shushan	Fertil Steril	Human menopausal gonadotropin and the risk of epithelial ovarian cancer
25	Case-Control	1997	Chang	Cancer	Perineal talc exposure and risk of ovarian carcinoma
26	Case-Control	1997	Cook	Am J Epidemiol	Perineal powder exposure and the risk of ovarian cancer
27	Case-Control	1998	Green	In J Cancer	Tubal sterilization, hysterectomy and decreased risk of ovarian cancer.
28	Case-Control	1998	Godard	Am J Obstet Gynecol	Risk factors for familial and spordic ovarian cancer among French Canadians: A case-contr study
29	Case-Control	1999	Cramer	International J of Cancer	Genital talc exposure and risk of ovarian cancer
30	Case-Control	1999	Wong	Obstet Gynecol	Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study
31	Case-Control	2000	Ness	Epidemiol	Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer
32	Case-Control	2004	Pike	Fertil Steril	Hormonal factors and the risk of invasive ovarian cancer: A population based case contro study
33	Case-Control	2004	Mills	Am J Epidemiol	Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California
34	Case-Control	2008	Goodman	Endcor Relat Cancer	Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk
35	Case-Control	2008	Gates	Cancer Epid Bio Prev	Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer
36	Case-Control	2008	Merritt	Int J Cancer	Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer
37	Case-Control	2009	Moorman	Am J Epidemiol	Ovarian cancer risk factors in African-American and white women
38	Case-Control	2009	Wu	Int J Cancer	Markers of inflammation and risk of ovarian cancer in Los Angeles County
39	Case-Control	2011	Rosenblatt	Gynecol Oncol	Mineral fiber exposure and the development of ovarian cancer
40	Case-Control	2012	Lo-Cignaic	Epidemiol	Aspirin, non-aspirin non-steroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer
41	Case-Control	2012	Kurta	Cancer Epid Bio Prev	Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control stu
42	Case-Control	2015	Wu	Cancer Epid Bio Prev	African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after considering nongenetic risk factors and oophorectomy rates
43	Case-Control	2016	Schildkraut	Cancer Epid Bio Prev	Association between body powder use and ovarian cancer: the African American Cancer epidemiology Study

Table 4. List of Included Studies with Number of Cancers, Controls, and Reported Odds Ratios

	Study Type	Year	Author	Cancers	Controls or Cohort Size	Odds Ratio	95% CI
1	Cohort Study	2000	Gerting	307	78,630	1.12	(0.82,1.55)
2	Cohort Study	2010	Gates	797	108,073	1.06	(0.89, 1.28)
3	Cohort Study	2014	Houghton	427	61,576	1.12	(0.92,1.36)
4	Cohort Study	2016	Gonzalez	154	41,654	0.73	(0.44,1.2)
5	Systematic Review	1992	Harlow *	1,106	1,756	1.30	(1.1, 1.6)
6	Systematic Review	1995	Gross	1,333	2,362	1.29	(1.02, 1.63)
7	Systematic Review	2007	Huncharek	1,858	2,830	NA	NA
8	Systematic Review	2003	Huncharek	5,260	6,673	1.33	(1.16, 1.45)
9	Systematic Review	2008	Langseth			1.35	NA
10	Systematic Review	2010	IARC			1.30	
11	Systematic Review	2017	Berg	15,230	NR	1.22	(1.13, 1.30)
12	Systematic Review	2018	Penninkilampi	14,311	NR	1.31	1.24, 1.39
13	Pooled Data	2013	Terry	4,472	6,175	1.37	(1.19-1.58)
14	Pooled Data	2016	Cramer	2,041	2,100	1.38	(1.01,1.99)
15	Case-Control Study	1982	Cramer	215	215	1.58	(0.98, 2.47)
16	Case-Control Study	1983	Hartge	135	171	2.50	(0.70, 10.0)
17	Case-Control Study	1988	Whittemoore	188	539	1.45	(0.94, 2.22)
5	Case-Control Study	1989	Harlow	116	158	1.10	(0.70,2.1)
18	Case-Control Study	1989	Booth	235	451	1.30	(0.80,1.9)
19	Case-Control Study	1992	Harlow	235	239	1.80	(1.1, 3.0)
20	Case-Control Study	1992	Rosenblatt	77	46	1.70	(.70, 3.9)
21	Case-Control Study	1992	Chen	112	224	3.90	(0.9,10.6)
22	Case-Control Study	1993	Tzonous	189	200	1.05	(.28, 3.98)
23	Case-Control Study	1995	Purdie	824	860	1.27	(1.04, 1.54)
24	Case-Control Study	1996	Shushan **	200	408	2.00	NA
25	Case-Control Study	1997	Chang	367	564	1.51	(1.13,2.02)
26	Case-Control Study	1997	Cook	313	422	1.60	(0.9, 2.9)
27	Case-Control Study	1998	Green	824	855	1.30	(1.1, 1.6)
28	Case-Control Study	1998	Godard	170	170	2.49	(0.94,6.56)
29	Case-Control Study	1999	Cramer	563	523	1.60	(1.18, 2.15)
30	Case-Control Study	1999	Wong***	499	755	1.13	(0.89, 1.43)
31	Case-Control Study	2000	Ness	767	1,367	1.50	(1.1, 2.0)
32	Case-Control Study	2004	Pike				
33	Case-Control Study	2004	Mills	256	1,122	1.74	(1.14, 2.64)
34	Case-Control Study	2008	Goodman	367	602	0.99	(.70, 1.41)
35	Case-Control Study	2008	Gates			1.41	(1.14, 1.76)
36	Case-Control Study	2008	Merritt	1,576	1,509	1.34	(1.06, 1.68)
37	Case-Control Study	2009	Moorman	1,086	1,057	1.37	(1.05, 1.80)
38	Case-Control Study	2009	Wu	609	688	2.08	((1.34 3.23)
39	Case-Control Study	2011	Rosenblatt	812	1,313	1.13	(0.93,1.36)
40	Case-Control Study	2012	Lo-Cignaic	902	1,802	1.34	(1.07,1.66)
41	Case-Control Study	2012	Kurta	902	1,802	1.41	(1.16, 1.69)
42	Case-Control Study	2015	Wu	1,701	2,391	1.46	(1.27,1.69)
43	Case-Control Study	2016	Schildkraut	584	745	1.71	(1.26, 2.33)

Odds ratio, likelihood (odds) that an outcome will occur because of a particular exposure compared to the likelihood it will occur without the exposure. 95% CI, 95% confidence interval, a measure of statistical uncertainty that says with about 95% of the time that the true value is within the range of numbers. The wider the range, the higher the uncertainty. NR, not reported.

* crude unadjusted estimate

** approximate, unadjusted estimate

*** assessed perineal or thigh use, and controls all have cancer

Berge (2018) [68]
This large, comprehensive systematic review of the association between genital use of talc powder products and ovarian cancer also had well-described methods. Berge reviewed and abstracted data for 27 publications and reported an overall summary estimate of the association between talc exposure and ovarian cancer. For six of the reviewed studies, Berge included data published in a pooled data analysis, from Terry [69] described below) that had not been previously included in the original publications. Overall, data on 15,230 women with ovarian cancer were analyzed (a number that is incorrectly reported in the paper). This is slightly higher than the number included in Penninkilampi because of the additional patients from the Terry publication. The summary estimate for risk of ovarian cancer for women who ever used genital talc was RR 1.22 (95% CI 1.13, 1.30). When stratified by histologic type, serous carcinoma was the only type with a significant association to talc use (RR 1.24, 95% CI 1.15, 1.34). There was no difference in risk when tumors were categorized as invasive versus borderline.

To assess relationships among ovarian cancer and intensity and duration of use, these measures were analyzed separately rather than as a combined measure that would give an estimate of the total number of exposures; the analyses did not demonstrate a significant dose response. Importantly, these measures were assessed only in five studies with the results on frequency of use presented as increased risk per additional day per week of talc use, which assumes a very linear association. I was not able to identify the original studies used in the review that reported the results with this level of granularity. Because of the small number of studies, the results (3% increase in risk per additional day of talc used, with high statistical uncertainty) were not surprising.

The authors also stratified the results by the study design (as did Penninkilampi) and found that the association between talc exposure and ovarian cancer was significant only for the case-control studies, although, as above, the cohort studies had the weakest definition of exposure. The primary limitation of the review is defining exposure as ever having used talc. As described above, this is a broad, vague definition that probably dilutes any estimated association, as it includes both women with trivial use and with regular use. A second limitation is that the included studies adjusted for a variety of covariates although this is unavoidable in this type of summary. The large difference in general between adjusted and crude results emphasizes the importance of adjustments when estimating particular risk.

Langseth (2008) [70]
This systematic review of the association between genital use of talc powder products and ovarian cancer included 21 publications. The overall pooled odds of cancer were OR 1.35 across all studies. Several authors of this systematic review were involved in an IARC report on talc exposure. They analyzed a subset of eight studies used in the IARC report that were considered to be the most informative for estimating ovarian cancer risk. Analysis of these more relevant, higher quality studies, produced an increased ovarian cancer risk of 30 to 60% (presumably OR 1.3–1.6) associated with talcum powder use. This subset analysis did not document a dose response or assess associations by cancer types.

Huncharek (2007) [71]
Huncharek summarized the results of nine studies that reported on the association between talc used on contraceptive diaphragms and ovarian cancer. No data on perineal talc exposure were analyzed and the data are not included herein. Of note, the reported methodological details suggest a very poorly designed and conducted study. Some of the included papers do not even mention talcum powder products used with diaphragms. This systematic review is poor quality.

IARC (2006) [62]
Beginning in 1969 the International Agency for Research on Cancer (IARC) began a program to critically review the data on the carcinogenic risk of chemicals to humans. They subsequently expanded their reviews to included evaluation of carcinogenic risks associated with a range of exposures (including risks associated with biological and physical agents, lifestyle factors, complex mixtures of exposures, occupations, etc.) The purpose of the IARC program is to elaborate and publish detailed monographs including critical review of data, to evaluate human risks, and to indicate where uncertainty exists and where additional data are needed. They also give an overall assessment of the strength of the associations. It is worth noting that the individuals who contribute to IARC reports (the Working Group) include extremely knowledgeable and unbiased scientists who have specific content expertise and who have no apparent conflicts of interest. Invited specialists and representatives from international health agencies are brought in to supplement the scientific experts. In their evaluation, they heavily weight whether data support a conclusion of causality. They score evidenced into four categories, ranging from a) evidenced suggesting lack of carcinogenicity; b) inadequate evidence of carcinogenicity c) limited evidence of carcinogenicity and d) sufficient evidence of carcinogenicity. Category c is used when there is possibly carcinogenicity, and this category is not used lightly. An exposure meets category c if there is a positive association between observed exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance of bias or confounding could not be ruled out. They further categorize agents into 3 groups: Group 1, corresponding to d above (sufficient evidence), the agent is carcinogenic to humans; Group 2, which includes 2A (the agent is probably carcinogenic) and 2B: the agent is possibly carcinogenic to humans. A review focused on the risks associated with carbon black, titanium oxide and talc was published in 2006. The review included a detailed review of the individual studies examining perineal talc use as a risk factor for cancer. IARC concluded that perineal use of talc-based body powder is possibly carcinogenic to humans (Group 2B)

Huncharek (2003) [72]
This review of 16 studies assessed the relationship between genital exposure to talc and ovarian cancer using data for 5260 women with cancer and 6673 controls. The pooled OR for ever being exposed to perineal talc powder products was 1.33 (95% CI 1.16, 1.45). Small differences were observed in the estimated ORs by whether controls in the case-control studies were from hospital populations (OR 1.19, 95% CI 0.99, 1.4), or the general population (OR 1.38, 95% CI 1.25, 1.52). I believe these differences are small. In general, in case-control

studies, population controls are likely more relevant and valid. However, as with several of the other reviews, talcum powder exposure was assessed as any exposure rather than quantifying by intensity. No stratification by tumor subtype or invasiveness was performed.

Gross (1995) [73]
Gross reviewed 10 studies on the association between talc exposure and ovarian cancer using data on 1333 women with cancer and 2362 without cancer. To summarize the RR of malignant epithelial cancer types due to any exposure to talc, adjusting for ovarian cancer risk factors, the authors combined results from five studies for OR 1.29 (95% CI 1.02, 1.63). For an analysis of all cancers (borderline and invasive), they included data from seven studies for a similar OR of 1.31 (95% CI 1.08, 1.58). Notably, the authors did not provide any methodological details of how they identified, assessed, and combined studies, making the results difficult to fully interpret. As with several of the other reviews, they assessed any exposure to talc.

Harlow (1992) [74]
Harlow reviewed five previously published studies and summarized an OR, not adjusted for confounding factors, and added his own data for a crude estimated OR of 1.3 (95% CI 1.1, 1.6). Unfortunately, no methodological details were provided on how studies were identified, assessed, and combined or how exposure was defined, making the results difficult to fully interpret. Further, only the combined, estimated, non-adjusted crude OR was reported. Of note, the results of the five published studies used in the review (in contrast to the summary) are well described and of good methodological quality.

Systematic Reviews: Summary
The systematic reviews provide a remarkably consistent estimate of an approximately 30% increase in the risk of ovarian cancer associated with any talc powder products use. The studies summarized in the systematic reviews reported consistent results with little variability and closely overlapping estimates for ovarian cancer risk due to talc use. Further, the reviews suggest that the risks are greater for invasive serous cancer. I believe Penninkilampi provides a comprehensive and high quality review and his estimate is that women who regularly use talc powder products, defined as >3600 lifetime applications, have a 40% increased risk of ovarian cancer compared to women with no regular talc power product use. The association was significant for serous cancers.

While the methodological approaches of these systematic reviews were generally valid, I believe they all shared the weakness of focusing on any talcum powder use rather than daily talcum powder use, and this motivated my own review (below).

<u>Pooled Data</u>
Two large studies pooled data from several studies. They are worth describing because of their larger sample size and strong methodology in comparison to the individual case-control studies.

Pooled Data 1: Terry (2013)[69]
This report pooled data on ovarian cancer patients from a national research consortium and assessed the relationship between talc powder products exposure and ovarian cancer by histologic subtype and invasiveness. Data were from eight case-controlled studies and importantly included previously unpublished data. The authors tried to unify definitions across the studies, but the definitions nonetheless varied widely. The prevalence of genital powder use in the controls varied widely across participating study sites, ranging from 15%–45%, suggesting either large variations in the underlying populations or, probably more likely, variation in the definition of powder use that led to these differences.

The data were for a total of 8525 cases and 9859 controls in the primary analysis. The authors found that **genital talcum powder use was associated with an approximately 24% increased risk of epithelial ovarian cancer (OR 1.24, 95% CI 1.15, 1.33).** When stratified by cancer type, the risk was increased for all cancers except mucinous cancer. Risks were approximately equally elevated for invasive and borderline tumors. They used a subset of patient data to determine RR of ovarian cancer for the highest talcum powder users, measured as cumulative lifetime perineal applications (defined as applications per month and months of the year). They also considered age (inclusion in the highest user group required more use at age 70 than age 40) and assessed risk of cancer among the highest users. **The odds of cancer in the highest talc exposure category was higher than for women who ever used talc (OR 1.37, 95% CI 1.19, 1.58).** A significant dose response was seen when data on all patients were analyzed, with greater exposure leading to greater risk.

Pooled Data 2: Cramer (2016) [75]
Cramer conducted several case-control studies on the relationship between genital talc powder use and ovarian cancer. He pooled data from a large number of these studies, described as reflecting study enrollment in 1992–1997, 1998–2002, and 2003–2008. This publication reports the analysis of pooled data from these separate enrollment phases and a more detailed characterization of those data. Cases were women who resided in Eastern Massachusetts and New Hampshire diagnosed with epithelial ovarian cancer between the ages of 18 and 80. Controls were women identified through random-digit dialing, driver's license lists and town resident lists. Women were interviewed in person, and details of talc use were elicited including the number of applications per month (allowing assessment of frequency of use), timing of use, and lifetime exposures. These descriptions gave far greater detail than most other reports and are thus an important contribution to the field. Further, more demographic and clinical history were obtained and described in these enrollments than for other reviewed studies. This report gave associations from pooled data for 2041 cases and 2100 controls. The larger size of the population, unified variables, and greater detail about cases and controls allowed a larger number of stratifications than other studies.

Overall, genital talc use was associated with an OR of 1.33 (95% CI 1.1.6, 1.52). An important observation was that risk decreased with time since last use. Thus, how often women regularly used talcum powder (daily, or weekly or monthly) was meaningful for predicting ovarian cancer risk, but not if the women had not used talcum powder for 5 or more years.

Women who reported using talcum powder daily (>30 applications per month) had an OR of 1.46 (95% CI 1.2, 1.78). Of note, among women in the ovarian cancer case group who used talcum powder, daily was the most commonly reported frequency of use**. When analysis used data on women who reported their total number of talcum powder applications, those in the highest group category (>7200 lifetime applications, the equivalent of 20 years of daily application) had an OR for ovarian cancer of 1.49 (95% CI 1.06, 2.1).**

Cramer conducted detailed analysis of factors that could influence/interact with the association between talcum powder and ovarian cancer. Some of the results are quite striking. First, a very strong interaction with race was noted. **African-American women seem to be at a particularly elevated risk of ovarian cancer following talcum powder exposure (OR 5.08, 95% CI 1.32, 19.6) compared with white women (OR 1.35, 95% CI 1.17, 1.55).** This finding calls for greater research given the higher incidence, and poorer outcomes among African American women. Asian women seem to be at reduced risk (OR 0.04, 95% CI 0.01, 0.34). **Analysis showed a strong relationship with menopausal status and use of hormone replacement therapy.** ORs were significantly increased in premenopausal women (OR 1.41, 95% CI 1.13, 1.75) and **postmenopausal women who used hormone treatment (OR 2.21, 95% CI 1.63, 3.0).** Postmenopausal women who did not use hormone therapy were not at increased risk of ovarian cancer (OR 1.0, 0.68, 1.49). **Interestingly, the risk of ovarian cancer among postmenopausal hormone-treatment users was elevated only if they used hormones before hysterectomy and tubal ligation but risk was substantial (OR 3.49, 95% CI 1.39, 8.75) if talcum powder was used before these surgeries (OR 5.85, 95% CI 2.89, 11.9) compared to talcum powder use both before and after surgery.**

These findings merit further assessment in other populations but raise the possibility that estrogen is important in ovarian carcinogenesis. The authors also stratified analyses by histologic type and found that the relationship between ovarian cancer and frequency of talcum powder use was significantly elevated for invasive and borderline serous cancer and invasive endometrioid cancer, but not for mucinous, clear cell or mucinous borderline cancer. **Among the most frequent users of talc the adjusted OR for invasive serous cancer is 1.54 (95% CI 1.15, 2.07).** This relationship was even stronger among premenopausal women (OR 1.85, 95% CI 1.21, 2.8) compared to postmenopausal women (OR 1.33, 95% CI 0.96, 1.85).

Pooled Data of Case-Control Studies: Summary
The increased risk of ovarian cancer associated with talc use was estimated at around 40% across these studies. The increased risk for serous cancer was even higher at 50%.

Case-Control Trials
A large number of case-control studies are published—too many to dedicate a paragraph to summarizing the methods of each.
21,24,36,40,74,76-99

I carefully read and abstracted data from each study. Without assessing the quality of the case-control studies, I included them in a table and sorted them by size of the reported effect

of talc on ovarian cancer risk. It's a way to get an overview of what they report – and Viewing them in this way is easy to see the general direction of the effect. All but two demonstrate a positive association (OR > 1) between any talc powder products use and ovarian cancer, with ORs ranging from 0.73–3.9 across studies, Table 5 .

Table 5: List of Case-Control Studies Sorted by Estimated Effect Size (Odds Ratio)

Year	First author			Odds ratio	Confidence interval
	2008	Goodman	367	602	0.99 (.70, 1.41)
1993	Tzonous	189	200	1.05	(.28, 3.98)
1989	Harlow	116	158	1.10	(0.70,2.1)
1999	Wong*	499	755	1.13	(0.89, 1.43)
2011	Rosenblatt	812	1313	1.13	(0.93,1.36)
1995	Purdie	824	860	1.27	(1.04, 1.54)
1989	Booth	235	451	1.30	(0.80,1.9)
1998	Green	824	855	1.30	(1.1, 1.6)
2008	Merritt	1576	1509	1.34	(1.06, 1.68)
2012	Lo-Cignaic	902	1802	1.34	(1.07,1.66)
2009	Moorman	1086	1057	1.37	(1.05, 1.80)
2008	Gates			1.41	(1.14, 1.76)
2012	Kurta	902	1802	1.41	(1.16, 1.69)
1988	Whittemoore	188	539	1.45	(0.94, 2.22)
2015	Wu	1701	2391	1.46	(1.27,1.69)
2000	Ness	767	1367	1.50	(1.1, 2.0)
1997	Chang	367	564	1.51	(1.13,2.02)
1982	Cramer	215	215	1.58	(0.98, 2.47)
1997	Cook	313	422	1.60	(0.9, 2.9)
1999	Cramer	563	523	1.60	(1.18, 2.15)
1992	Rosenblatt	77	46	1.70	(.70, 3.9)
2016	Schildkraut	584	745	1.71	(1.26, 2.33)
2004	Mills	256	1122	1.74	(1.14, 2.64)
1992	Harlow	235	239	1.80	(1.1, 3.0)
1996	Shushan **	200	408	2.00	NA
2009	Wu	609	688	2.08	((1.34 3.23)
1998	Godard	170	170	2.49	(0.94,6.56)
1983	Hartge	135	171	2.50	(0.70, 10.0)
1992	Chen	112	224	3.90	(0.9,10.6)
2004	Pike			NA	

V. Rationale for and Explanation of the New Systematic Review

In previous systematic reviews that I have conducted, I have obtained the most meaningful and consistent results by narrowly defining the research topic of the review, including only studies that provide data on this narrow topic in a well-defined population and stratifying my analysis of the studies' results by relevant factors such as age or race/ethnicity. The benefit of this approach is more accurate, precise, and meaningful results, while the potential tradeoff is a reduction in general applicability of the results, because many studies may be excluded for inadequate data. I believe greater accuracy is more important because I want to be certain about the data I am describing. For example, when I conducted a systematic review on the use of transvaginal ultrasound as a diagnostic test for endometrial cancer, I initially stratified

the results by patient use of hormone therapy. The reviewed studies had consistent results, but only if profoundly different diagnostic criteria were applied for women who did and did not use hormone therapy. For this reason, I completed one review on hormone users and another on non-users. In this case, I had sufficient data to assess both groups.

In this review on talcum powder use, I had sufficient data to summarize results for regular users of talcum powder (as close to daily but reflecting use of talc powder products several times per week) and risks of serous cancer; I did not have sufficient data to summarize results for occasional users or risk of other cancer types. I believe the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer. I want to point out that this does not mean that other uses (i.e. less than approximate daily use) does not cause ovarian cancer, nor that talc powder products does not cause other types types of ovarian cancer (e.g. endometrioid cancer). Thus, for the systematic review below of case-control studies on the relationship between perineal exposure to talcum powder products and ovarian cancer, I focused on whether regular use of perineal (genital) talc increases the risk of the ovarian cancer. When possible, I focused on the most common and serious type, invasive serous ovarian cancer.

VI. New Systematic Review of Literature Quantifying Association Between Regular Frequent Genital (Perineal) Talcum Powder Products Application and Ovarian Epithelial Cancer Risk with A Focus on Invasive Serous Cancer.

Literature Search

I performed a literature search to identify primary research studies (not reviews) that included patient-level data on the association between talc and ovarian cancer. The literature search was performed in the Medline, Embase, and Scopus databases using keywords "ovarian cancer," "talc," "perineal powder" and "genital powder." Abstracts of resulting publications were reviewed to identify if they addressed the topic and included data. Only English-language articles were reviewed. The references of identified articles and reviews were scanned to identify additional publications. Review articles, editorials, letters to the editor were excluded.

Article Selection

Articles were included based on relevance to the question: **Does the regular (as close to approximately daily)** use of genital (perineal) talcum powder increase invasive epithelial ovarian cancer? Because daily use was the most dominant use category, when studies stratified their results into quartiles of use, or lifetime applications, I included the highest use category that had a reasonable number of data points to reflect daily use. Wherever possible, data on invasive serous cancer were abstracted separately. When I found duplicate reports on the same patient group, the largest and most detailed publication was included. This usually meant the most recent publication, but not always. An important caveat is that I could not always identify duplicative results. I included data from the Terry 2013 pooled data study because it included new data from previous studies. I also included data from the Cramer

2016 pooled analysis and earlier publications with duplicative patients were not included. But I calculated the results both including and excluding these studies.

Exclusion

Studies were not included if they reported only crude ORs unadjusted for confounding factors, A few studies were excluded because, the research methods were poorly defined, even though they reported on women who frequently used talcum powder. Studies that asked participants a single question about ever use of talcum powder, without further quantification of exposure, were not included in the summary.

Defining Talcum Powder Products Use

Regular use was defined ideally as daily or at least more than 3 uses per week. I also accepted studies that defined use as "regular" where the description made it clear that this was regular use. Studies that reported "regular use" but defined it as use of less than this frequency, were not included. Regular use was selected to differentiate occasional use (which may include one-time or infrequent use or use during only a particular time of a woman's menstrual cycle) from sustained regular use. Studies that asked participants a single question about ever use of talc, without further quantification of exposure, were not included in the summary. For example, Purdie reported that 52–57% of women reported ever using talc without further quantification and was not included. Several studies asked about *regular use* defined as at least once a month. These studies were not included unless they further characterized women into different categories of use; if so, I included data for women in the highest use category as long as this was group was large enough to be meaningful. When studies asked about ever use but defined use and stratified results by use, I included any data that may have reflected daily use. This measure of regular use is imprecise but is more accurate and meaningful than evaluating talcum powder exposure as any use.

Stratification of Analyses: Focus on a Single Histologic Type Where Possible

My review focused on invasive serous cancer where possible, but also included all invasive cancer. The decision to focus on a single histologic cancer type was in part because ovarian cancers include a broad range of types and association of talc and ovarian cancer might differ by type. I chose serous cancers because they are most common invasive ovarian cancer type. Importantly, serous ovarian cancer is the only histologic type for which most individual research studies accumulated sufficient cases for valid statistical analysis. This cancer type also has the least uncertainty in pathological diagnosis (see Section III, Histologic Types). Further and most importantly, serous ovarian cancer is the most aggressive histologic type, so identifying causal factors is important. Finally, I focused on invasive cancer (as opposed to borderline cancer) because the risk of death from invasive serous tumors is far higher than for noninvasive types, with growing consensus that borderline tumors may not be malignant.

Type of Exposures

Studies were included if they reported on perineal exposure (rather than exposure through sanitary napkins, diaphragms, or condoms) as this is the most common exposure type and is

likely to reflect the most consistent exposure. I did not exclude studies if they reported combined use, as long as the exposure included perineal use.

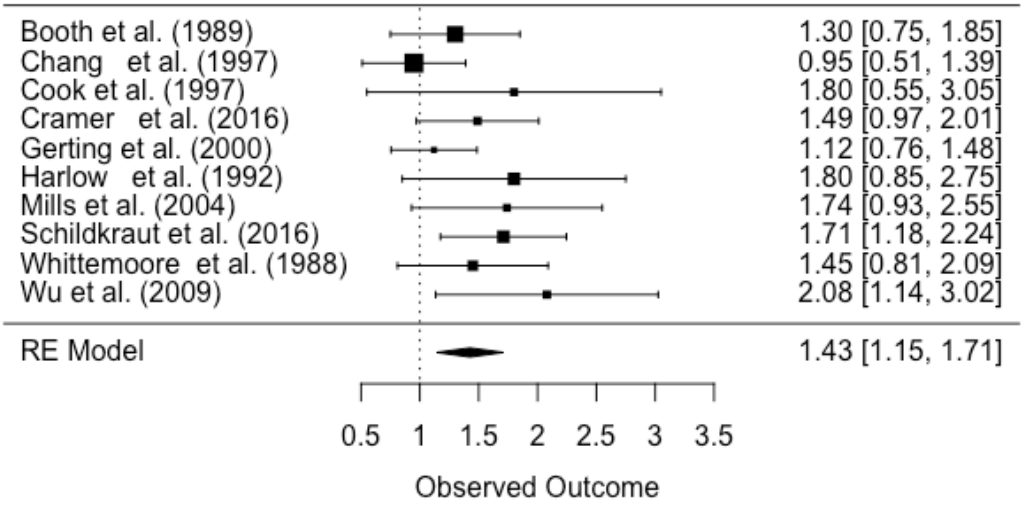
Statistical Analysis

Two individuals (Smith-Bindman and a consultant biostatistician) reviewed an abstracted data from each publication. Differences were resolved by consensus. The focus of the review was on quantifying the association between regular talcum powder products use and ovarian cancer, with a sub analysis on serous cancer and invasive cancer. Meta-analysis was performed using the metafor package in R (Version 3.5.1). The rma function was used to apply linear mixed effects models to study results and calculate summary statistics on effect size. Due to varying amounts and types of available data from each included publication, adjusted odds ratios (OR) and standard errors were used as the model inputs. Standard error (SE) was estimated using the relationship: 95% confidence interval = Effect size +/- 1.96*SE, assuming a roughly normal distribution of data and roughly symmetrical upper and lower confidence interval bounds. Incorporating adjusted ORs and SE into models in this way provides the added benefit of allowing model use of covariate-adjusted data (versus crude OR data). Weighting was done based on estimates of inverse variance. Study result heterogeneity was estimated based on maximum likelihood methods and was summarized via an I2 statistic and associated p-value. The decision to include results from the cohort study by Gertig and colleagues (2000), which reported relative risk (RR), was based on the estimation that the RR value was only nominally different from the OR, a safe assumption in a study sample where less than 0.4% of the cohort developed the condition-of-interest.

Results

Overall 10 studies reported on daily talc powder products use and the risk of ovarian cancer. These studies were homogenous, and the odds of ovarian cancer associated with regular use was 1.43 (95% CI 1.15 1.71). The included studies with associated point estimates are shown in a Forrest Plot in Figure 2

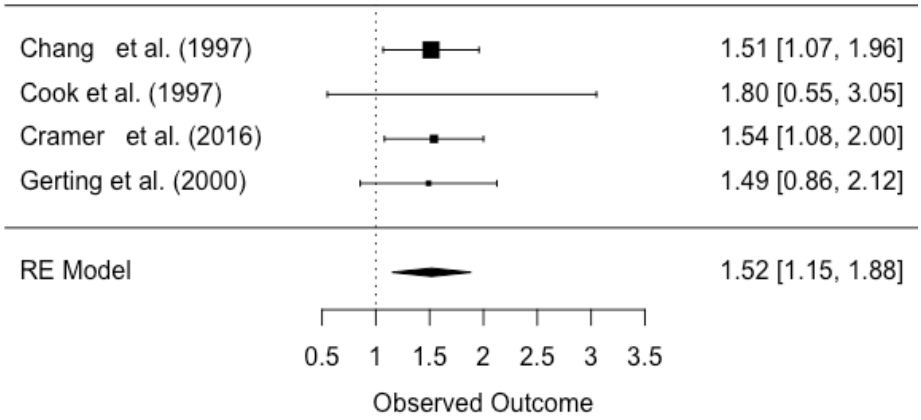
Figure 2. Forrest plot showing odds of ovarian cancer associated with regular use of talcum powder products.



The primary analysis of this excluded Terry, but the results were nearly identical if Terry was included

There were studies reported on regular talcum powder use and invasive serous cancer (or all invasive cancer if serous not reported) These studies were homogenous. The odds of invasive serous cancer associated with regular use was 1.52 (95% CI 1.15, 1.88). The results were similar when assessing the odds of all serous cancer.

Figure 3 Forrest plot showing odds of ovarian cancer assocated with regular use of talcum powder products and invasive serous cancer.



New Systematic Meta-Analytic Review: Summary

The results of my systematic review of case-control studies on talcum powder use and ovarian cancer risk were consistent and indicate a **50% increase in risk of serous invasive cancer related to routine talcum powder exposure compared to no exposure**. This review had limitations including that study results were self-reported. I tried to be consistent in defining exposure, but this factor was subjectively determined by the individual studies. I tried to eliminate overlap of participant populations used in the included studies, but some patients may have contributed data to more than one study.

Overall Summary of the Epidemiology Data Describing the Association Between Talcum Powder Products and Serous Ovarian Cancer

I conclude, based on the review of the available primary studies, systematic reviews and my own quantitative review, that regular exposure to talcum powder products increases ovarian cancer risk by around 50%. The existing systematic reviews (in particular Penninkilampi and Berge) also concluded a significant increase in ovarian cancer risk following talcum powder exposure.

VII. Other Relevant Factors

Research Supporting Talcum Association with Ovarian Cancer: Transit to Ovary and Risk Reduction on Interruption

Evidence from relevant studies is clear that talcum powder particles applied to the genital region will ascend through the vagina and fallopian tubes and enter the pelvic cavity, reaching fallopian tubes and ovaries. In humans, this route has been established experimentally by labelling inert particles, applying them to the perineum just prior to planned hysterectomy, and then recovering them from the fallopian tubes following surgery. [Egli Fertil Stwril 1961]

Further, talc particles have been found in normal and malignant ovarian tissue. Henderson found that in 10 of 13 tested epithelial ovarian cancer tumors, 75% had talc embedded in the tissue. This result confirms that talc reached to the areas with cancerous tissue, but not that it caused the cancer. Histological evaluation of ovaries removed because of ovarian cancer or benign conditions have identified both talc particles and asbestos fibers in the ovarian tissue, further supporting that particles applied to the perineum reach the ovaries. [60,100] Heller found that in all women in a study who were having ovaries removed for benign ovarian growth had talc in their ovaries. These results confirm that talcum powder applied to the perineum may be absorbed into the vagina and migrate or be transported to the tubes and ovaries. [101-104] In 1967, Graham and Graham demonstrated that intraperitoneal application of asbestos in guinea pigs and rats results in overgrowth of ovarian epithelial cells comparable to the histologic changes in epithelial ovarian tumors in women. The greater frequency at which talc particles are discovered in ovarian cancerous tissue than in normal ovarian tissue further supports that these particles may be causing cancer.

Several epidemiological studies evaluated the risk of ovarian cancer associated with talcum powder products before and after women had tubal ligation or hysterectomy, which surgically removes the route by which talc reaches the ovaries. The studies strongly suggest that the increased risk of ovarian cancer associated with talcum powder products use is reduced or eliminated after tubal ligation or hysterectomy. The results support that the risk from talcum powder products is elevated when women have an open pathway from the perineum to the ovary that enables powder components to reach the ovaries via unobstructed fallopian tubes., The collective results demonstrate that talcum powder products are carcinogenic through direct transport/migration to the fallopian tubes and ovaries.

Variation in Risk when Talc Use is Discontinued

Several studies showed that the risk of ovarian cancer associated with talc powder products decreases as the time from discontinuation of powder use increases. For example, Cramer found an elevated risk of ovarian cancer with talc powder products use and the risk decreased as time since last use increased. [75]

VIII. Consideration of Causality of Talc Powder Products and Ovarian Cancer : Bradford Hill Analysis

Causality is easiest to determine in studies such as randomized controlled trial, in which participants are randomized to receive or not receive a treatment, then their health is followed to see their response. However, people cannot ethically be randomized to be exposed to a potentially cancer-causing agent. Therefore, when assessing risk factors for cancer, the Bradford Hill Factors are often used. They provide a framework for assessing the weight of evidence to help decide if causality is likely, given a particular association, such as between talcum powder and ovarian cancer. The guidelines are imperfect and provide a framework as compared with an absolute set of criteria.

I address each of the Bradford Hill factors below, with my understanding of how the evidence of talcum powder products exposure supports or refutes causality. While the Bradford Hill Factors include nine aspects of association, they should not be used as a checklist for causation. Instead, they can help interpret associations and aid in inferring causality. For each factor, I have highlighted why I believe this factor is more or less important.

A) Strength of Association

It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, I do not believe this is necessarily the case. If a risk factor increases the risk of disease by 50%, and the exposure is common, it will have a far greater impact on a number of people, in comparison to a rare exposure that has a higher associated OR. And if the association is truly one that increases risk by 50%, then this is the magnitude of the association that will be detected. It is not intuitive that if an exposure increases a risk by 50%, this difference is not discoverable compared with an exposure that increases risk by 100%. A larger association between exposure and disease may be easier to identify, but I do not believe it is more likely to indicate causality or importance.

As an example, Table 6 shows an overview of the relationship between bladder cancer and two of its known risk factors; occupational industrial chemicals and smoking. Several industrial chemicals such as 2-naphthylamine are strongly associated with bladder cancer risk. In 1954, Case et al. reported a 200-fold increased bladder cancer risk for workers exposed to 2-naphthylamine. In cohort studies of rubber industry workers, elevated standardized mortality ratios (SMRs) as high as 253 (95% CI 93, 551) were reported. Use of some of these chemicals are now prohibited in Europe and their use is regulated in the United States because they cause cancer.(OSHA, 2011).

Cigarette smoking is also a known bladder cancer risk factor. However, the RR for smoking and bladder cancer is around 3, and therefore about 100 times lower than the RR for exposure to industrial chemicals. Yet bladder cancer is the second most common cancer attributed to smoking in the United States. It impacts a very large number of individuals. Of the 70,000 cases of bladder cancer diagnosed each year, as many as 60% are estimated as attributable to smoking.

Using the RR magnitude to quantify the "importance" of these two risk factors, industrial chemicals and smoking, would be misleading. Smoking will result in far more cancers than industrial chemicals, even though the RR is much lower. In the crude data in Table 6, of the approximately 70,000 bladder cancers diagnosed annually in the United States, 50,000 are thought to result from cigarettes while fewer than 1000 result from occupational exposures. A 50% reduction in smoking exposure will save 25,000 men from getting bladder cancer. Reducing industrial chemical exposures will saving around 500 men from getting bladder cancer. Thus, any impact on reducing known exposures for bladder cancer has the potential to be around 50 times more impactful if directed at smoking.

Table 6. An example showing the number of individuals who might be impacted through exposure to an occupational chemical that leads to bladder cancer as opposed to smoking.

	Occupational Exposure 2-naphthylamine	**Smoking**
Estimated odds ratio associated with exposure	200	3
Number of individuals exposed annually	10,000	50,000,000
Bladder cancers due to exposure annually	**1000**	**50,000**
Impact on number of cancers diagnosed annual if exposure reduced by 50%	**500**	**25,000**

The bladder cancer example highlights that a factor that increases risk by 50% will have an enormous impact on population mortality if the exposure is common or if the cancer is particularly lethal. This is certainly the case for talcum powder products, which are used by as many as half of all women in the U.S. Women's use of talcum powder products is so widespread that even a relatively modest increase in risk would pose a sizeable health risk to the population. Further, a 50% risk increase is particularly important for ovarian cancer, which has a high mortality rate, with rare early detection.

Defining a "strong" association is critical for assessing potentially causal relationships. A current concept in epidemiology is that considerations about whether a factor causes a disease should weigh statistical validity and significance and the multiple factors that influence the disease. Thus, assessing *strength of association* when inferring causality requires examining underlying research and analytic methods, comparing the weight of evidence in the literature, and considering other contextual factors. The data supporting the causality of talcum powder products exposure for ovarian cancer is extremely strong.

Using the existing evidence, I reviewed and assembled for this report, I estimated how many ovarian cancers that occur each year in the United States are likely to be caused by exposure to talcum powder products in comparison to other risk factors for ovarian cancer, Table 7. This is a relatively simple analysis, but nonetheless is informative. The total number of ovarian cancers that are estimated to occur in the US annually is 22,240, and these will occur among

the 50.8 percent of the U.S. population of 311 million who are women. Of these ovarian cancer cases, approximately half (11,120) will reflect invasive serous carcinoma. For the purpose of this simple analysis, I have assumed that the elevation in ovarian cancer risk associated with talcum powder product exposures occurs only with invasive serous carcinoma. This is not true, but the data are the most certain for these cancer and this is a conservative assumption (meaning the true number of cancer and proportion of cancers caused by talcum powder product users will be even higher than my calculation). A proportion of ovarian cancers will occur among women who regularly use talcum powder products, and the remainder will occur in women who do not regularly use talcum powder products. If we estimate that women who use talcum powder products regularly have a 50% elevated risk of invasive serious cancer and we estimate the number of women who are exposed to daily talcum powder products is between 10% and 30% (this proportion is fewer than ever users of talcum powder products), then between 1,589 and 4,351 women will be diagnosed each year with invasive serous cancer caused by the exposures, reflecting between 14% and 39% of all invasive serous cancers and reflecting between 7% - 20% of all ovarian cancer diagnosed each year. This is a tremendous risk. This is a very large number of cancers to be caused by a product that provides no medical benefit. This Bradford Hill Factor of the Strength of the association is important and is met.

Table 7 An estimate of the number of ovarian cancers and invasive serous cancers caused by regular use of perineal talc powder products.

Proportion of women who regularly use Talcum powder products	Annual Invasive Serous Cancer in Women Exposed to Talcum Powder Products	Annual Invasive Serous Cancer in Women Not Exposed to Talcum Powder Products	% Invasive Serous Cancer in Women Exposed to Talcum Powder Products	% of all ovarian Cancer in Women Exposed to Talcum Powder Products
10%	1,589	9,531	0.14	0.07
20%	3,033	8,087	0.27	0.14
30%	4,351	6,769	0.39	0.20

B) Consistency of Associations in Different Populations and Studies

Another consideration for association and causality is consistency of the data. The data on the association between genital talc and ovarian cancer are highly consistent. The relative stability in the estimated increase in the risk of ovarian cancer associated with talc powder products use (50% increase for regular users of talcum powder and serous cancers; around 40% increase for all epithelial ovarian cancer and regular users of talcum powder products), as assessed across time and in diverse populations with diverse study designs, strongly argues that the causal association is real and satisfies the Bradford Hill guideline for consistency of associations across populations and studies.

C) Specificity Between Cause and Effect

The Bradford Hill factors suggest that associations are more likely to be causal when an exposure causes only one disease. While some examples of highly specific exposures and outcomes exist, many exposures and health concerns involve complex chemical mixtures and low-dose environmental and occupational exposures complicated by a variety of personal risk factors. A recent review stated, "The original criterion of *specificity* is widely considered weak or irrelevant from an epidemiologic standpoint." [105] Asbestos, for example, is associated with a range of cancers and various exposures. Regardless of doubts about the meaningfulness of this factor, talcum powder products are primarily associated with ovarian cancer and thus fulfills the specificity consideration, although this consideration is not one of the most important considerations for causality in my expert opinion.

D) Temporality

An exposure must come before an outcome for the exposure to be causal. Bradford Hill explained that for an exposure-disease relationship to be causal, exposure must precede the onset of disease. While this is self-evident, in epidemiological studies, reverse causality, in which behavior related to a health issue is influenced by knowledge or events about the issue, is always a concern. For example, women who undergo ovarian cancer treatment may begin using talcum powder products during their pre- and post-operative period because of symptoms or side effects perceived to be alleviated by talcum powder products use. Assessing talcum powder use without specifying the time of use might lead to women with ovarian cancer being more likely to report talcum powder products use. In this example, talcum powder may not have caused the cancer; rather, use of talcum powder products was caused by the cancer (and treatments). The importance of this issue led to Bradford Hill's consideration of temporality when assessing causality.

In essentially all of the case-control studies that assessed use of talcum powder products, women were specifically asked to report talc powder products only during past, not current periods; thus, the studies explicitly assessed exposure to talcum before cancer. Typically, questions were phrased "Did you ever use talc, but not in the last year before cancer diagnosis?" to exclude the year prior to diagnosis. This issue is not relevant for the included cohort studies, as women were surveyed about their exposures prior to cancer ascertainment. Thus, the temporality consideration is important for my consideration and is satisfied.

E) Dose Response

In general, when risks are proportional to exposure (e.g., doubling exposure doubles risk) this dose-response evidence is considered to support causality. Many of the reviewed studies did not collect sufficient data to carefully quantify the dose response, and many limited their comparisons to an ever/never comparison. This is in part what motivated me to complete my separate quantitative review to at least be able to dis-entangle ever into regular versus not regular use. The reviewed studies that did provide data that could be used to assess the

potential for dose response had mixed results in quantifying dose response. While most studies showed evidence of a dose response, others did not. For example, Schildkraut showed that >20 years of any genital powder use (OR 1.51, 95% CI 1.11, 2.06) showed a stronger association with ovarian cancer than <20 years of use (OR 1.33, 95% CI 0.95, 1.86). [99] Terry and Harlow showed significant dose responses, where ORs increased as exposures increased. [69,74] The adjusted ORs increased from 1.3, to 1.5 to 1.8 with <1000, 1000–10,000, and >10,000 lifetime applications. Overall, any exposure to talcum powder resulted in an OR of 1.5; direct perineal application had an OR of 1.7 (95% CI 1.1, 2.7), daily exposure had an OR of 1.8 (95% CI 1.1, 3.0) and women with an intact genital tract who were estimated to have had more than 10,000 applications during ovulating years had the highest risk (OR 2.8 95% CI 1.4, 5.4). This exposure was found in 14% of women with ovarian cancer. Penninkilampi [67],the most comprehensive of the systematic reviews, also showed a dose response where women with more than 3600 lifetime applications had slightly higher risks as did women who reported long-term (>10 years) talc use. In contrast, Whittemore [77] showed no dose response, and Booth [78] demonstrated the reverse—the higher the dose, the lower the risks. The data from reviewed studies were too diverse to summarize a dose-response relationship. The measures of exposure frequency and duration varied, and the studies used different thresholds for quantifying exposures. Further, the measures to quantify dose tended to be crude, making the response even more difficult to establish.

In summary, most but not all studies of talcum powder products and ovarian cancer show a dose response, but the results are inconsistent, and more importantly, are not considered or assessed in most of the published studies. A dose-response relationship is not required for causality and in large part because data were not consistently available, this factor does not weight heavily in my consideration. Further, this factor did not weight heavily in my considerations in that not all exposures will have a dose response, and some will indeed have a threshold effect. This is important here because asbestos is believed to exhibit a threshold, rather than a linear, dose-response.

F) Biologic Plausibility: Factors Linking Talc and Ovarian Cancer

The epidemiological evidence suggests a strong and positive association between exposure to talcum powder products and invasive ovarian cancer. However, epidemiological evidence alone does not provide a mechanism or pathophysiological process that accounts for the increased risk. Nor does the epidemiological evidence confirm the specific component or ingredient in talc powder products that is responsible for carcinogenesis. Nonetheless, the data are persuasive that particles contained in talcum powder reach the tubes and ovaries, inflammation initiate a causal pathway, and that several components of talc powder products including asbestos, asbestiform fibers in talc, and heavy metals can contribute to the carcinogenicity of the products. This was a strong factor in my consideration of the evidence because there is extremely strong evidence that the components of talc powder products are known to be highly carcinogenic in other settings.

G) Coherence and Consistency with Understood Biology

The guideline of coherence is considered similar to biological plausibility. For both, the cause-and-effect explanation should be consistent with all knowledge available. For talcum powder and ovarian cancer, this consideration is easily satisfied.

H) Experimental Evidence

The evidence in humans of the impact of talcum powder products exposure and ovarian cancer development is based on a large number of observational studies. Direct experimental evidence in the form of randomized controlled trials in humans is simply not possible to generate, for ethical reasons. The experimental evidence in humans that talc particles can migrate to the ovary and be incorporated into ovarian tissue is relevant to developing a causal model but does not directly prove that that exposure causes cancer. There is also human data relating to the inflammatory nature of ovarian cancer. There is compelling in vitro research delineating the inflammatory mechanism by which talcum powder causes cancer. Animal studies showing inflammatory tissue effects and tumor formation with talcum powder exposure are also supportive.

I) Analogy

Bradford Hill implied that when evidence is strong of a causal relationship between a risk factor and disease, researchers should be more accepting of weaker evidence that a similar risk factor may cause a similar disease. Thus, analogy has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar. The strong evidence for the association between asbestos and lung cancer, and the chemical similarity between these minerals, as well as their fibrous nature, supports the analogy consideration and causal inference.

Summary: Consideration of Causality of Talc Powder Products and Ovarian Cancer using Bradford Hill

In consideration of Bradford Hill, the clear strength of the association (A), remarkable consistency in the published literature across a large number of populations and research studies (B), temporality (D) considered in all of the published studies, and perhaps most importantly, biological plausibility (F) were the criteria that I considered of paramount importance when assessing the causality of exposures of talc powder products and epithelial ovarian cancer

IX. Conclusion

In conclusion, substantial evidence supports a strong, positive and causal association between ovarian cancer and genital exposure to talcum powder products. Regular exposure to talcum powder products causes ovarian cancer in some women. This opinion is based on my extensive review of the medical and scientific literature, my own independent meta-analysis of the data, and my experience and expertise in the areas of epidemiology and women's health, including ovarian cancer.

All opinions are made to a reasonable degree of medical and scientific certainty. I reserve the right to amend or supplement this report as new information becomes available.

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98. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2015;24(7):1094-1100.
99. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2016;25(10):1411-1417.
100. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *American journal of industrial medicine.* 1996;29(5):435-439.
101. Egli GE, Newton M. The Transport of Carbon Particles in the Human Female Reproductive Tract. *Fertility and sterility.* 1961;12(2):151-155.
102. Sjosten AC, Ellis H, Edelstam GA. Retrograde migration of glove powder in the human female genital tract. *Human reproduction (Oxford, England).* 2004;19(4):991-995.
103. Venter PF, Iturralde M. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde.* 1979;55(23):917-919.
104. RE J. Jones, Richard E., and Kristin H. Lopez. "Human Reproductive Biology - 4th Edition Chapter 9 - Gamete Transport and Fertilization." In Human Reproductive Biology, Third., 159–73. San Diego: Academic Press, 2006. https://doi.org/10.1016/B978-0-12-382184-3.00009-X. MAS Project #14-1683, Analysis of William E. Longo, PhD and Mark W. Rigler, PhD (April 28, 2017).
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Exhibit A

CURRICULUM VITAE
REBECCA SMITH-BINDMAN, MD

Title Professor, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences, Phillip R. Lee Institute for Health Policy
Director, Radiology Outcomes Research Lab, University of California San Francisco

Address: Department of Radiology and Biomedical Imaging
350 Parnassus Ave, Suite 307
San Francisco, CA 94117
Voice: 415 353-4946**;** Fax: 415 353-2790
Email: Rebecca.Smith-Bindman@ucsf.edu

EDUCATION

1980 - 1985	Princeton University	BSE	Engineering / Architecture
1985 - 1986	Columbia University		Post Bacc Pre-Med
1987 - 1991	University of California, San Francisco	MD	Medicine
1991 - 1992	University of California, San Francisco	Intern	Pathology
1992 - 1996	University of California, San Francisco	Resident	Radiology
1996 - 1997	University of California, San Francisco	Clinical Instructor	Radiology, Ultrasound
1996 - 1998	University of California, San Francisco	Fellow	Epidemiology & Biostatistics

LICENSES, CERTIFICATION

1992	California Medical License # G76462
1993	California X-ray Supervisor and Operator License RHL 143658
1996	Board Certification, American Board of Radiology

PRINCIPAL POSITIONS HELD

1998 - 2003	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Assistant Professor
2003 - 2009	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Associate Professor
2009 - current	UCSF, Radiology and Biomedical Imaging, Epidemiology and Biostatistics, Obstetrics, Gynecology and Reproductive Sciences	Professor
2014 - current	UCSF, Phillip R. Lee Institute for Health Policy Studies	Member
2000 - current	UCSF, Radiology Outcomes Research Lab	Director

OTHER POSITIONS HELD CONCURRENTLY

1999 - 2000	St Bartholomew's and The Royal London School of Medicine	Research Fellow
2009 - 2010	NIH, National Cancer Institute, Radiation Epidemiology Branch	Research Scientist

HONORS AND AWARDS

1985	Cum laude, Princeton University
1985	Senior Thesis Prize, Princeton University
1991	Student Summer Research Fellowship, Institute for Health Policy Studies, UCSF
1999, 2000	Nycomed Amersham Fellow, Radiologic Society of North America
2007	Nomination, Clinical Research Mentor of the Year, Bay Area Symposium on Clinical Research
2010	Nomination, CTSI Consultant of the Year, Impact Award
2010	Scientific Paper of the Year, Minnies, Auntminnie.com
2010	Finalist, Most Influential Radiology Researcher, Minnies, Auntminnie.com
2011	Leader in Imaging, Auntminnie.com
2012	Finalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2012	Semifinalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2012	Winner, UCSF Center for Health Care Value, Medical Center Initiative, Innovation Award
2013	Finalist, Scientific Paper of the Year, Auntminnie.com, Minnies
2013	Runner-up, Scientific Paper of the Year, Auntminnie.com, Minnies
2013	Paper honored as 1 of the top 10 publications Funded by NCI's Epidemiology and Genomics Research Program
2014	Invited Editor, J of the American College of Radiology, March 2014, Radiation Dose Optimization
2014	Among Philip R. Lee Institute for Health Policy Studies faculty videos on UCTV, "Is Medical Imaging Harmful to Health: Opportunities to Influence Health Policy", most popular, N = 409,937
2015	Academy of Radiology Research, Distinguished Investigator Award
2015	Election to Fellowship, Society of Radiologists in Ultrasound

KEYWORDS AND AREAS OF INTEREST

Health Services Research, Outcomes Research, Disparities Research, Women's Imaging, Comparative Effectiveness Research, Quality Improvement, Dissemination and Implementation Sciences, Evidenced Based Radiology, Assessment of Population Impact of Screening Tests, Radiation Associated with Medical Imaging, Radiation as an Environmental Cause of Cancer, Management of Incidental Findings on Diagnostic Testing

OVERVIEW

Narrative

Dr. Smith-Bindman is a clinical researcher with expertise in health services research, epidemiology, outcomes research, comparative effectiveness research, and dissemination and implementation sciences focused on diagnostic imaging. Her research has focused on evaluating the quality, utilization, accuracy, predictive values and impact of diagnostic testing on patient health, and has quantified both the risks and benefits of medical imaging when used in different contexts and by different populations. One area of focus has been on evaluating racial and ethnic differences in access and utilization of screening mammography and how that contributes to higher breast cancer mortality among African American women, and on factors that influence the quality and access to screening among vulnerable populations (see references 33, 34, 37, 43, 46, 48, 61, 67 at the end of CV). A separate area of focus has been on quantified the variation in radiation dose associated with medical imaging across patients and institutions, and quantified the impact of radiation, particularly from computed tomography, as an environmental carcinogen. (see references 53, 58, 60, 62, 65, 68, 69, 72, 76, 78, 79., 81, 87, 89, 91, 97, 102, 107.) Separate from her research activities, she has been actively involved in translating evidence into changes in practice and policy. She has *informed policy leaders, practitioners and the public about* the safety concerns surrounding the use of radiation in imaging by describing the issue in main stream media, testifying before the US Congress, and by advising the FDA, The Joint Commission, the International Atomic Energy Agency, the International Council on Radiation Protection and leading professional societies. She has also written quality measures focused on radiation safety, and her work has resulted in organizations which monitor health care quality to adopt measures of diagnostic imaging safety.

Significant Publications

1. **Smith-Bindman** et al. Ultrasound vs Computed Tomography for Suspected Nephrolithiasis NEJM. 2014; 371:1100-10
2. Miglioretti DL, Johnson E, William SA, Grenlee RT, Weinmann S, Solberg LI, Feigelson HS, Roblin D, Flynn MJ, Vanneman N, **Smith-Bindman R**. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 167 (88): 700-7
3. **Smith-Bindman R**, et al. Risk of Thyroid Cancer based on Thyroid Ultrasound Imaging Characteristic: Result of A Population Based-Study. JAMA Internal Medicine. 2013 173(19):1788-96
4. **Smith-Bindman R.** Appendix F. Ionizing Radiation Exposure to the US Population, with a Focus on Radiation from Medical Imaging, included in Breast and the Environment: A Life Course Approach. The Institute of Medicine. March 20 2012
5. **Smith-Bindman R et al.** Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. JAMA Internal Medicine 2009;169(22):2078-86
6. Curtis E, Quale C, Haggstrom D, **Smith-Bindman R**. Racial and Ethnic Differences in Breast Cancer Survival: How Much Is Explained By Screening, Tumor Severity, Biology, Treatment, and Co-morbidities. Cancer 2008 112(1):171
7. Goldman L, Haneuse S, Miglioretti D, Kerlikoswke K, Buist D, Yankaskas B, **Smith-Bindman R**, An assessment of the quality of mammography care at facilities treating medically vulnerable populations Medical Care 2008 46(7):701-8.
8. **Smith-Bindman et al.** Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med, 2006; 144(8):541-53
9. Haggstrom DA, Quale C, **Smith-Bindman R**. Differences in the Quality of Breast Cancer Care Among Vulnerable Populations. Cancer. 2005 Dec 1;104(11):2347-58.
10. **Smith-Bindman, R,** et al Endovaginal ultrasound to evaluate endometrial abnormalities. JAMA 1999;281:1693-4

PROFESSIONAL ACTIVITIES

CLINICAL

Attending physician, Ultrasound Section, Department of Radiology and Biomedical Imaging, UCSF, 25%. Includes supervised instruction of residents and fellows. My teaching focuses on how to use evidence to help inform interpretation of clinical examinations.

PROFESSIONAL ORGANIZATIONS

Memberships

1997 - 2018	Society of Radiologists in Ultrasound (SRU)
1997 - 2018	Radiology Alliance for Health Services Research in Radiology (RAHSR)
2013 - 2018	American College of Radiology (ACR)
2014 - 2018	American Roentgen Ray Society (ARRS)
2014 - 2018	Association of University Radiologists (AUR)

Service to Professional Organizations (selected)

2010 - 2011	American Board of Medical Specialties, American Board of Radiology, American College of Radiology, and Physician Consortium for Performance Improvements. Patient Radiation Dose Work Group
2011 - 2012	Institute of Medicine Committee on Breast Cancer and the Environment, commissioned report “Temporal Changes in lonizing Radiation and Estimate of Contributions to Breast Cancer,” contributing author
2012	Centers for Disease Control and Prevention, Cancer Prevention Work Group
2012 - 2014	The Joint Commission, Diagnostic Ionizing Radiation and Magnetic Resonance work group focused on issues of safety and guideline development
2012 - Present	International Council on Radiation Protection (ICRP) Task Group #79 on Defining Effective Dose Use in Medicine
2014	International Atomic Energy Agency (IAEA) United Nations General Assembly and Security Council. Special Committee Considering Population Impact of Low Dose Radiation
2015	Council of Distinguished Investigators of the Academy of Radiology Research

Service to Professional Publications (selected)

2000 - 2018	Journal of the American Medical Association (JAMA)
2000 - 2018	JAMA Internal Medicine
2000 - 2018	New England Journal of Medicine (NEJM)
2000 - 2018	Radiology
2000 - 2018	American Journal of Radiology
2000 - 2011	Journal of the National Cancer Institute
2000 - 2011	Health Affairs

2000 - 2015	Health Services Research
2000 - 2010	American Journal of Obstetrics & Gynecology
2000 - 2010	American Journal of Public Health
2000 - 2010	Annals of Internal Medicine
2000 - 2010	Journal of Medical Screening
2000 - 2010	Journal of Women's Health
2000 - 2010	Medical Care
2000 - 2010	Medical Decision Making
2000 - 2010	Obstetrics and Gynecology
2000 - 2010	Ultrasound in Obstetrics & Gynecology

INVITED PRESENTATIONS

International

2001	US - UK Cancer Learning Network, Deprivation and Cancer, *London, United Kingdom*
2001	British Society of Human Genetics, Prenatal Screening for Down syndrome in England and Wales and Birth Outcomes, *London, United Kingdom*
2002	Global Summit on Mammographic Screening, Europe Institute of Oncology, U.S.-U.K. Comparison of Screening Mammography, *Milan, Italy*
2005	University of Copenhagen, Does Practice Make Perfect; Association Between Volume and Accuracy of Mammography, *Copenhagen, Denmark*
2006	International Society for Prenatal Diagnosis, Prenatal Screening for Down syndrome in The Second Trimester of Pregnancy, *Kyoto, Japan*
2009	Canadian Breast Cancer Foundation, Forum on the Earlier Detection and Diagnosis of Breast Cancer, *Toronto, Canada*
2010	Nation Cancer Research Institute (NCRI), Risk of Cancer from Computed Tomography Examinations, *Liverpool, United Kingdom*
2013	Bach Mai University Hospital, Radiation for Medical Imaging: A Hidden Epidemic, *Hanoi, Vietnam*
2014	International Atomic Energy Agency (IAEA), Health Effects of Exposure to Low Dose Ionizing Radiation Associated with Medical Imaging, *Vienna, Austria*
2014	Korea College of Radiology, Tracking and Monitoring Radiation Dose and Its Impact Across the University of California Medical Centers and CT Radiation Doses Are Not What You Think: Why It's Important to Monitor and Track Dose Seoul, Republic of Korea
2016	International Atomic Energy Agency (IAEA), Exposure to low dose ionizing radiation from medical imaging and the health effects from these exposures. International Atomic Energy Agency. Technical Meeting on Science, Technology and Society Perspectives on Nuclear Science, Radiation and Human Health: The View from Asia, Singapore University
2016	University of North Carolina School of Medicine, Chapill Hill, NC, Radiology Department Grand Rounds , Diagnostic Imaging: Increasing Effectiveness and Safety Radiation From Medical Imaging,

2016 Singapore General Hospital, Singapore. Radiology Grand Rounds. Visualizing Patients and Their Dose to Improve Health Care Quality,

2016 St Luke's International Hospital, Tokyo, Japan. Hospital-wide grand rounds, Radiation from Medical imaging: A Hidden Epidemic.

2017 Childhood Leukemia International Consortium, Annual Meeting, Minneapolis, Minnesota, Estimating Radiation Exposure from Imaging Procedures

2017 Charity Hospital, Berlin, Germany. Radiology Grand Rounds, Radiation from Medical Imaging: A Hidden Epidemic

2017 Charity Hospital, Berlin, Germany, Imaging for Suspected Nephrolithiasis: Results from the Randomized Controlled Trial

2017 University Hospital, Basel, Switzerland, Radiology Grand Rounds. A Dose of Reality: The Need for Active CT Dose Management

2017 Center for Diagnostic Imaging Quality Institute Council of Medical Directors, Scottsdale, AZ Keynote: Radiation from Medical Imaging

2017 The Leap Frog Group Pediatric Computed Tomography Radiation Dose

2017 PCORI Advisory Panel on Communication and Dissemination Research Presentation UCSF CT Radiation Dose Registry to Ensure a Patient-Centered Approach for Imaging

2017 American Urological Association (AUA) Quality Improvement Summit, Baltimore Maryland Keynote Address. Imaging Wisely: Improving the Value of Medical Imaging

2018 Jakarta Radiology Society, Jakarta Indonesia. Dose Optimization Implementation to achieve better radiology service in HospitalKeynote Addresses: Radiation from Medical Imaging: A Hidden Epidemic and Optimizing Radiation Doses for CT

2018 Westmead Hospital Sydney Australia. Radiology Grand Rounds. Radiation from Medical Imaging: A Hidden Epidemic

2018 Westmead Childrends Hospital, Sydney Australia. Optiizing Radiation Doses For Pediatric CT

National

2000 American College of Medical Genetics

2000 Society of Radiologists in Ultrasound

2000 Society for Health Services Research in Radiology

2001 Society of Radiologists in Ultrasound Annual Meeting

2001	Society for Health Services Research in Radiology
2002	Society of Radiologists in Ultrasound
2003	Breast Cancer Surveillance Consortium
2003	Society of Radiologists in Ultrasound
2003	Centers for Disease Control and Prevention
2003	RSNA 88th Scientific Assembly and Annual Meeting
2004	Institute of Medicine (IOM): Saving Women's Lives
2004	Breast Cancer Surveillance Consortium
2005	Improving Mammographic Quality Standards Institute of Medicine (IOM)
2006	Beth Israel Deaconess Medical Center, Grand Rounds
2006	National Institute Child Health and Human Development
2007	National Cancer Institute, National Institute of Health (x2)
2008	Mount Sinai Urban Health Institute; Metro Chicago Breast Cancer Taskforce, Partnerships in Translation: Advancing Research and Clinical Care
2008	University of Washington, Seattle, Washington, Grand Rounds, and Visiting Professor,
2008	HMO Research Network Conference (4th annual), Danville, Pennsylvania
2009	Society of Radiologists in Ultrasound, National Conference on Management of Ovarian Cysts
2009	Canadian Forum for the Earlier Detection and Diagnosis of Breast Cancer
2010	Center for Disease Control & Prevention, Annual Cancer Registry Meeting, Atlanta, Georgia
2010	HMO Research Network conference, Emerging Frontier in Healthcare, Research Delivery, Austin, Texas
2010	National Council on Radiation Protection (NCRP), Communication of Radiation Benefits and Risks in Decision Making
2010	National Cancer Institute, Board of Scientific Advisors, Bethesda, Maryland
2010	American Statistical Association Conference on Radiation Health, Annapolis, Maryland
2010	Breast Cancer Surveillance Consortium Annual Meeting, Washington, D.C.
2010	Kaiser Permanente: National Radiology Leadership Group, held at the RSNA, Chicago, IL
2011	Cleveland Clinic, Health Care Quality Innovation, Cleveland, Ohio
2011	Auntminnie.com, Live WebEx Conference RADEXPO 2011
2011	University of New Mexico, Visiting Professor, External Reviewer, Resident Research Day
2011	Oregon Health Sciences University, Department of Emergency Medicine, Grand Rounds
2012	Society for Imaging Informatics for Medicine (SIIM), San Francisco, CA
2012	Brown University, Grand Rounds, Emergency Medicine, RI Hospital, Providence, RI
2012	Society for Imaging Informatics in Medicine (SIIM), Los Angeles, CA

2012	PharmMed OUT, Georgetown University, Washington, DC
2012	Agency for Healthcare Research and Quality, Rockville, MD
2012	Radiology Society of North America, expert witness in full day mock trial focused on radiation safety and whether radiologists need to communicate risks to patients, Chicago, IL
2012	University of Pennsylvania, Grand Rounds, Emergency Medicine, Philadelphia, PA
2013	Radiology Society of North America (RSNA), Controversies Session, CT Radiation and Risk: How Certain Are We of the Uncertainty? Chicago, IL
2013	American Cancer Society, Doc Talk Lecture Series
2013	Association of University Radiologists (AUR), Comparative Effectiveness and Patient-centered Outcomes Research, Los Angeles, CA
2014	Cancer.net Podcast, "CT Scans and Cancer Risk", Available Online at http://www.cancer.net/blog/2014-10/ct-scans-and-cancer-risk
2014	Oregon Chapter, American College of Emergency Physicians, Portland, Oregon
2015	Women in Government Foundation (non-profit, non-partisan organization of all U.S. female state legislators) Diagnostic Imaging. Increasing Its Effectiveness and Safety, at 16th Annual Southern & Eastern Regional Conference, Charleston S Carolina
2016	Lindeberger Cancer Center, University of North Carolina, Chappil Hill NC, Radiation From Medical Imaging: A Hidden Epidemic
2017	American Urological Association (AUA) Quality Improvement Summit, Baltimore Maryland Keynote Address. Imaging Wisely: Improving the Value of Medical Imaging

Regional Presentations (selected)

2000	Kaiser Permanente Department of Genetics, Oakland CA
2001	San Francisco State University, SF CA
2001	UCSF, San Francisco General Hospital, Department of Medicine, Grand Rounds
2001	American College of Obstetrics and Gynecology
2002	UCSF Breast Oncology Program Comprehensive Cancer Center Grand Rounds
2003	UCSF Obstetrics and Gynecology Grand Rounds, SF CA
2004	UCSF Multi-Department Symposium. Racial Disparity and Breast Cancer, SF CA
2004	UCSF Quality of Breast Cancer Care Symposium, SF CA
2005	Sisters Network, San Francisco (African American Advocacy Organization)
2005	Stanford University, Department of Health Research and Policy, Grand Rounds, Palo Alto CA
2006	UCSF, Lunch and Learn: San Francisco Community Outreach, SF CA
2006	Bay Area Health Care and Quality Outcomes, San Francisco, CA
2007	California Breast Cancer Research Symposium, Los Angeles, CA
2010	Bay Area Clinical Research Symposium, Plenary Speaker, San Francisco CA

2011	UCSF Department of Medicine Grand Rounds, San Francisco, CA
2011	San Francisco General Hospital Department of Medicine, Grand Rounds, San Francisco, CA
2011	UCSF, Department of Urology Grand Rounds, San Francisco, CA
2011	UCSF Department of Radiology Grand Rounds, San Francisco, CA
2011	Eden Hospital, Department of Medicine Grand Rounds, Alameda, CA
2011	Stanford Hospital, Department of Medicine, Grand Rounds, Palo Alto, CA
2011	Kaiser Permanente Medical Center, Multi-departmental Grand Rounds, San Francisco, CA
2011	UCSF Institute for Health Policy Studies, San Francisco, CA.
2012	Kaiser Permanente Medical Center, Grand Rounds, San Francisco, CA
2012	Kaiser Permanente Medical Center, Grand Rounds, Oakland, CA
2012	Massachusetts General Hospital, Department of Emergency Medicine, Grand Rounds Boston,
2012	Beth Israel Hospital, Department of Emergency Medicine Grand Rounds, Boston, MA
2012	Univ. of California Office of the President, Quality Improvement and Technology, Oakland, CA
2012	UCSF, Department of Radiation Oncology, Grand Rounds,
2012	Southern California Kaiser Radiology Chiefs Grand Rounds,
2014	UCSF, Endocrine Grand Rounds, San Francisco, CA
2015	California Society of Radiology Technologists, Annual Meeting, San Francisco, CA Keynote Address. Radiation from CT: A Hidden Epidemic. Strategies to minimize doses: What technologists can do?
2016	Society of Radiology in Ultrasound, Annual Meeting, Baltimore Maryland. Risk of Thyroid Cancer Based on Thyroid Ultrasound Imaging Characteristics
2016	UCSF, Breast Oncology Program, Radiation from Medical Imaging: A Hidden Epidemic and Approaches for Improving.
2016	UCSF Mini-Medical School Radiation Safety and Medical Imaging
2017	University of California Davis, Radiology Grand Rounds, Radiation from Medical Imaging; A Hidden Epidemic
2017	UCSF: Stand Up for Science: Panel Discussant

GOVERNMENT AND OTHER PROFESSIONAL SERVICE (selected)

2002 - 2003	CDC, National Breast and Cervical Cancer Early Detection Program, Planning Committee
2002 - 2005	Cochrane Collaboration Screening and Diagnostic Tests, Methods Working Group
2003 - 2003	Radiology National Boards, Examination Question Writer
2003 - 2010	National Cancer Institute, Physician Data Query (PDQ)

2004 - 2005	CDC, National Breast and Cervical Cancer Early Detection Program, Panelist, Committee on Assessment of Covered Benefits, Expert
2007 - 2010	California Health Benefits Review Program (CHBRP)
2008 - 2011	Center for Scientific Review, NIH, Health Services Organization and Delivery Study Section
2010 - 2011	American Board of Medical Specialties, American Board of Radiology, American College of Radiology, and Physician Consortium for Performance Improvements. Patient Radiation Dose Work Group
2010	Congressional Hearing, US House of Representatives, Energy and Commerce, Subcommittee on Health. Medical Radiation: An Overview of the Issues. Expert Witness
2010	Food and Drug Administration, Center for Devices & Radiological Health, National Meeting Focus on Radiation Safety, Presenter
2010 - 2011	National Quality Forum, Imaging Efficiently Steering Committee
2011 - 2012	Institute of Medicine Committee on Breast Cancer and the Environment, commissioned report “Temporal Changes in lonizing Radiation and Estimate of Contributions to Breast Cancer,” contributing author
2010 - 2011	Lung Cancer Screening with CT Evidence Review Committee. Multidisciplinary collaboration, including American Cancer Society, American College of Chest Physicians; American Society of Clinical Oncology & The National Comprehensive Cancer Network
2011 - 2016	International Council on Radiation Protection (ICRP), Task Group 79 on Defining Effective Dose Use in Medicine
2012	Congressional Hearing, US House of Representatives, Energy and Commerce, Subcommittee on Health, hearing on the Consistency, Accuracy, Responsibility, and Excellence in Medical Imaging and Radiation Therapy (The CARE Bill), Expert Witness
2012	Centers for Disease Control and Prevention, Cancer Prevention Work Group
2012 - 2014	The Joint Commission, Diagnostic Ionizing Radiation and Magnetic Resonance work group focused on issues of safety and guideline development
2013	Government Accountability Office: Medicare Imaging Accreditation Establishing Minimum National Standards and an Oversight Framework to Ensure Quality and Safety of Advanced Diagnostic Imaging Services, May 2013, Contributor
2014	International Atomic Energy Agency (IAEA) United Nations General Assembly and Security Council. Special Committee Considering Impact of Low Dose Radiation
2015	Council of Distinguished Investigators of the Academy of Radiology Research

UNIVERSITY AND PUBLIC SERVICE

Service Narrative

There are several activities to which Dr. Smith-Bindman has contributed. For seven years she participated in the NCI sponsored Physicians Data Query (PDQ), an NCI committee charged with presenting evidenced based, on-line, widely accessible and widely disseminated guidelines relating to cancer screening and diagnosis. She

participated in several activities related to breast cancer screening including acting as a reviewer for the CDC on assessing the guidelines for the National Breast and Cervical Cancer Detection Program, participating in coverage decisions, acting as reviewer and content expert for the CA Health Benefits Review Program analyzing several bills before the state legislature that would expand breast cancer screening to include MRI, and participating in the creation of several IOM Reports. She has participated in several community projects, such as acting on the board of an African American breast cancer advocacy group, and as a consultant to the Metropolitan Breast Cancer Task Force, charged with improving breast cancer mortality rates and racial disparities. During the last five years She has been very active in local, statewide and national efforts around improving radiation safety, including invited presentations to the FDA, testifying before the US Congress on two occasions, working with innumerable societies and government organizations on guidelines and submitting two endorsed quality measures on radiation safety to the National Quality Forum. Her involvement in service activities within the University have focused on increasing the quality and quantity of translational research through participation in several University-wide task forces. Dr. Smith-Bindman serves on several Medical Center Committees, focusing on improved oversight and stewardship around radiation, and projects to improve the efficiency and effectiveness with CT.

UNIVERSITY SERVICE (selected)

2001 - 2015	UCSF School of Medicine, Faculty Recruitment Committees, Radiology, Rad Onc, Medicine
2002	UCSF School of Medicine Dean's Leadership Retreat, Santa Cruz
2003	University of California, Blueprint for Regional Excellence in Breast Cancer Care
2003	UCSF School of Medicine Task Force, Future of UCSF and Mission Bay
2003	UCSF Medical Center, Hospital Exceptional Physician Award, Committee Co-Chair
2003 - 2004	UCSF School of Medicine Task Force, Physician Scientist Program Clinic-Based
2003 - 2005	UCSF School of Medicine Faculty Council
2005	UCSF School of Medicine, Dean's Leadership Retreat, Santa Cruz, CA
2005 - 2006	UCSF Department of Radiology Seminars and Presentation Committee
2005 - 2008	UCSF Department of Radiology Annual Research Symposium Abstract Review Committee
2005 - 2009	UCSF Department of Radiology, SEED Grant Review Committee
2006 - 2007	UCSF Pathways for Clinical and Translational Research
2008 - 2010	UCSF Pathways to Discovery, Clinical and Translational Research, Advisory Council
2007 - 2010	University of California, Office of the President, CA Health Benefits Review Program
2009 - 2017	UCSF, Radiation Safety Committee
2012 - 2014	UCSF Department of Radiology, Maintenance of Certification Committee
2012 - 2015	UCSF Medical Center, Center for Health Care Value
2013 - 2017	UCSF School of Medicine, Conflict of Interest Advisory Committee
2014 - 2016	UCSF Clinical Enterprise, Strategic Plan, Committee for Continuous Process Improvement
2015 - 2017	UCSF Clinical Enterprise, Utilization Management Committee

PUBLIC SERVICE

2003 – 2007	SF Sisters, an African American breast cancer advocacy group, board member
2008 - 2008	Metropolitan Chicago Breast Cancer Task Force, Chicago IL, unpaid consultant
2011 - 2014	National Quality Form, National Consensus Standard for Patient Safety. Measure Developer "UCSF CT Radiation Dose Patient Safety Measure" Measure endorsed
2015	National Quality Forum, Pediatric Measures. Measure Developer, "Pediatric Computed Tomography Radiation Dose" Measure endorsed

TEACHING AND MENTORING

Teaching Narrative

Dr. Smith-Bindman spends substantial time mentoring trainees in clinical research. The trainees have ranged in experience from high school students through mid-career UCSF faculty. The individuals have come from a broad range of departments at UCSF including Radiology, Internal Medicine, Hospital Medicine, Emergency Medicine, Obstetrics and Gynecology, and Urology, and have also come from the UCSF Medical School, The University of California Berkeley, and local SF high schools. On average, she meets with each trainee 1-2 hours per week while collaborating. An NIH Mid-Career Investigator Award (K24) supported her time mentoring these individuals.

She teaches in several formal classes in the department of Epidemiology and Biostatistics primarily targeted to post graduate students who are completing a master's degree in clinical research. She is actively engaged in teaching the Radiology residents and fellows while attending on the clinical service and provides frequent lectures to the Radiology residents focused at research methods; frequently teaches in courses organized by the UCSF Office of Continuing Medical Education for both radiology courses and courses within other medical specialties. The radiology courses focus on using evidence to interpret our studies (usually focused on ultrasound topics), the lectures for other medical specialties focused on how to use imaging more appropriately. As listed above, she also frequently gives grand rounds within UCSF, and nationally on using imaging more appropriately. Lastly, she organized and ran a large, ongoing, virtual symposium on Radiation Safety described below. Both the content and format of this meeting were novel.

TEACHING

Formal scheduled classes for UCSF students.

The first class listed is a course for UCSF Medical Students. The remaining are part of the coursework offered within the UCSF Masters in Clinical Research Program, Department of Epidemiology and Biostatistics

Year	Title	Role	Class Size
2002 - 2005	Epidemiology and Biostatistics, UCSF School of Med	Section Leader	20
2005	Introduction to Diagnostic Testing	Lecturer	18
2007 - 2008	Clinical Performance and Health Outcome Measurement	Lecturer	20
2011 - 2014	Translating Evidence into Policy: Theory and Design	Lecturer	30
2010 - 2015	Framing Research to Influence Policy	Lecturer	25

Post Graduate CME courses (1-5 lectures/meeting)

2001	UCSF Obstetrics and Gynecology Update, San Francisco, CA
2001	UCSF Primary Care Medicine, Aspen, CO
2001	Primary Care Medicine, Maui, HI
2001	Management of the Hospitalized Patient, San Francisco, CA
2001	Controversies in Women's Health, San Francisco, CA
2001	Diagnostic Imaging in Women's Health, San Francisco, CA
2001	MRI & Ultrasound Imaging, Lake Tahoe, CA
2002	Obstetrics and Gynecology Update, San Francisco, CA.
2002	17th Annual Primary Care Medicine: Concepts and Controversies, Aspen, CO
2002	10th Annual Controversies in Women's Health, San Francisco, CA
2002	Diagnostic Imaging in Women's Health, San Francisco, CA
2002	Diagnostic Imaging, Maui, HI
2002	Obstetical, Gynocological and Abdominal Ultrasound, San Francisco, CA
2003	Primary Care Medicine, Diagnostic Imaging in Women's Health, Maui, HI
2003	11th Annual Controversies in Women's Health, San Francisco, CA
2003	Diagnostic Imaging for Disease Prevention, San Francisco, CA
2003	46th Annual Diagnostic Radiology Postgraduate Course, San Francisco, CA
2003	OB/GYN and Abdominal Ultrasound, San Francisco, CA
2003	MRI and Ultrasound by the Lake, Lake Tahoe, CA
2004	Women's Imaging, Sonoma, CA
2004	Primary Care Medicine, Maui, HI
2004	Diagnostic Imaging in Clinical Practice, San Francisco, CA
2005	Obstetrical and Gynecologic Sonography, San Francisco, CA
2005	Radiology Spring Training, Scottsdale, Arizona
2005	Abdominal Imaging, Montreal and Quebec, Canada
2006	Controversies in Women's Health, San Francisco, CA
2006	Controversies in Breast Cancer Screening and Diagnosis, San Francisco, CA
2006	Cutting Edge Radiology, Diagnosis and Intervention, Vancouver, Canada
2008	Primary Care Medicine: Update 2008, San Francisco, CA
2008	Diagnostic Imaging in Women's Health, San Francisco, CA
2008	Obstetrical/Gynecological and Abdominal Sonography, San Francisco, CA
2009	Primary Care Medicine: Update 2008, San Francisco, CA

2009	Obstetrical/Gynecological and Abdominal Sonography Update, San Francisco, CA
2011	Imaging of Kidney Stones, San Francisco, CA, Director
2011	Primary Care Medicine, Principles & Practice, San Francisco, CA, Keynote
2011	39th Annual Advances in Internal Department of Medicine, San Francisco, CA, Keynote
2011	Controversies in Women's Health, Department of Medicine, San Francisco, CA, Keynote
2012	Updates on Imaging, Maui, Hawaii
2013	UCSF Otolaryngology Annual Conference, San Francisco, CA
2017	UCSF Practical Body Imaging, Kona, Hawaii

Other Teaching

Radiation Safety and CT: Virtual Symposium. Innovative on-line Interactive CME course targeted to physicians (radiologists and those who order imaging), technologists, medical physicists, and trainees. This was created as an on-line, free, virtual meeting focuses on radiation safety. The initial creation of this virtual meeting began in 2013. Creating the meeting involved creating a multidisciplinary, on line, virtual meeting with over 100 lectures (see list of lectures, now offered freely on line - http://rorl.ucsf.edu/speakers), 10 live interactive sessions/chat rooms and over 500 registrants enrolled in the meeting during the "live days", and ongoing attendees attend each month. The speakers at the meeting included numerous department chairs, the director of the Agency for Health Care Policy at the time, a US Congressman, leaders from numerous societies, The Joint Commission, The American Board of Internal Medicine Foundation, and innumerable scientific experts on diverse patient safety issues, and the meeting was an integration of diverse viewpoints and perspectives. Dr. Smith-Bindman directed this meeting and personally wrote and delivered 7 lectures for the meeting. The meeting was novel in format and content.

MENTORING

Pre-doctoral students directly supervised

Dates	Name	Program or School	Current Position
2004 - 2005	C. Kagay	UCSF Medical School	Radiologist, Private Practice
2005 - 2006	A. Ding	UCB/ UCSF MD/MPH	MGH
2005 - 2008	A. Venkatesan	UCSF Medical School	Resident, Stanford
2006 - 2007	E. Dinkelspiel	Urban High School	Student, Univ. of Chicago
2011 - 2015	J. Keegan	Lick Wilmerding High	San Luis Obispo College
2010 - 2015	P. Mehta	UC Berkeley/UCLA Med School	UCLA Medical School
2012 - 2013	J. Zhang	UC Berkeley	Senior
2014 summer	A. Fraser	University High	Georgetown College

Postdoctoral fellows and residents directly supervised

Dates	Name	Position	Current Position
1998 - 2000	M. Copanigro, MD	Radiology Resident / Fellow	Private Practice

1998 - 2000	N. Vincoff, MD	Radiology Resident / Fellow	Private Practice
2003 - 2004	E. Weiss, MD	OB GYN Resident	Private Practice
2003 - 2005	K. Schueler, MD	RORL Research Fellow	Private Practice
2003 - 2005	D. Haggstrom, MD	Internal Medicine Fellow	Indiana University, Faculty
2005 - 2006	K. Reid, MD	Internal Medicine Fellow	Emory Faculty
2005	A. Jensen	PhD student, Copenhagen	Faculty
2005 - 2006	B. Ching, MD	Radiology Fellow	Private Practice,
2005 - 2006	A. Cole, MD	Radiology Fellow	Private Practice
2005 - 2007	L. Goldman, MD	Internal Medicine Fellow	UCSF Faculty
2006 - 2010	J. Lipson, MD	Radiology T32 Scholar	Stanford Faculty
2007 - 2008	J Stengel, MD	Radiology Fellow	Private Practice
2007 - 2008	A. Heath, MD	RORL Research Fellow	Private Practice
2007 - 2009	R. Cho, MD	Radiology Fellow	Private Practice
2007 - 2009	D. Sellami, MD	Radiology Resident / Fellow	Private Practice
2008 - 2009	A. Kamath, MD	Radiology T32 Scholar	NYU Faculty
2009 - 2010	J Ching, MD	OB GYN Resident	Faculty
2009 - 2011	N, Brasic, MD	Radiology Fellow	UCSF Faculty
2010 - 2011	D. Sridhar, MD	Radiology Resident	Private Practice
2010 - 2012	P. Lebda, MD	Radiology Fellow	Cleveland Clinic Faculty
2010 - 2013	I. Burger, MD	Radiology Resident	Private Practice
2010 - 2013	G. Merry, MD	Radiology Resident	Private Practice
2011 - 2014	J. Mongan, MD PhD	Rad Resident / Fellow	UCSF, Faculty
2013 - 2014	S. Hou, MD	Radiology Resident	NYU Faculty
2013 - 2014	C. Lee, MD	Radiology Resident	UCSF Faculty
2013 - 2014	T. Morgan, MD	Radiology Resident	UCSF Faculty
2013 - 2015	LA Hampton, MD	Urology Resident / Fellow	Fellow, Wash U
2013 - 2015	V. Arasu, MD	Radiology Resident	Resident
2013 - 2015	N. Benedetti, MD	Radiology Resident	University of Wash Faculty
2014 - 2015	B Carpenter, MD	Radiology Fellow	UCSF Faculty
2014 - 2015	J. Hsu, MD	Radiology Fellow	Private Practice
2014 - 2018	J. Demb	Epidemiology	UCSF

Faculty Mentoring

Dates	Name	Department / Section	Current Position
2002 - 2005	John Shepherd, MD	Radiology / Musculoskeletal	UCSF, Faculty, Radiology
2004 - 2005	Elaina Curtis, MD	UCSF Visiting Fellow	Univer. of Auckland Faculty
2005 - 2006	John Stein, MD	Emergency Medicine	UCSF Faculty, Emerg Med
2005 - 2006	Max Wintermark, MD	Radiology / Neuro	UVA, Faculty, Radiology
2007 - 2013	Lauren Goldman, MD	Internal Medicine	UCSF, Faculty, Medicine
2008 - 2011	Larry Rand, MD	OBGYN / Maternal Medicine	UCSF, Faculty, OBGYN
2008 - 2014	Antonio Westphalen, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2009 - 2017	Liina Poder, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2010 - 2018	Ralph Wang, MD	Emergency Medicine	UCSF Faculty, Emerg Med
2014 - 2018	John Mongan, MD, PhD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2017	Cindy Lee, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2017	Tara Morgan, MD	Radiology / Abdominal Imaging	UCSF, Faculty, Radiology
2014 - 2018	Maureen Kohi, MD	Radiology / Interventional	UCSF, Faculty, Radiology
2015 - 2018	Ben Franc, MD PhD	Radiology / Nuclear Medicine	UCSF, Faculty, Radiology
2017 - 2018	Brian Haas MD	Radiology	UCSF, Faculty, Radiology

RESEARCH AND CREATIVE ACTIVITIES

Research Narrative

Dr. Smith-Bindman's research focuses on understanding the impact of diagnostic testing on patient outcomes. She is the director of the UCSF Radiology Outcomes Research Laboratory, and her team includes several programmers, biostatisticians, a developer, and a handful of epidemiologists who serve as project managers for the funded grants below. Her research expertise is in areas of epidemiology, technology assessment, outcomes research, comparative effectiveness research, health services research, and dissemination and implementation sciences focused on imaging. The research has focused on evaluating the quality, utilization, accuracy, predictive values and impact of diagnostic testing on patient health, and has quantified both the risks and benefits of medical imaging when used in different contexts and by different populations. I am leading several studies that assess and standardize the radiation dose used for CT scanning, in order to minimize doses, without loss of diagnostic accuracy. Additional current research is focused on putting systems-based solutions in place to standardize the use of imaging. For example, ongoing projects focus on improving decision support provided to physicians to help improve the use of testing, using evidence to drive and guide the change in practice, and determining the optimal surveillance strategy for the follow up of incidental findings seen on CT imaging. The research projects she leads, listed below, are typically collaborative, involving researchers from diverse clinical areas and who offer diverse methodological expertise.

RESEARCH AWARDS

Current

PI 07/02/2014 - 06/30/2019
NIH $1,140,000 direct/yr1
CT DOSE Collaboration: Partnership for Dose **$7,900,000 total**

Collaboration across the US and Europe to standardize and optimize the doses used for CT. The study uses a novel randomized controlled trial design to compare simple feedback to a multicomponent intervention as strategies to optimize doses. There are approximately 125 hospitals participating in the trial.

PI 09/02/2013 - 08/31/2016
PCORI (Patient Centered Outcomes Research Institute) $492,163 direct/yr1
CT Radiation Dose Registry to Ensure a Patient Centered Approach for Imaging **$2,069,365 total**

Collaboration across the US and Europe to create benchmarks and standards for CT by pooling data from a large number of hospitals and outpatient facilities

PI 3/01/2015- 02/28/2020
NIH $1,834,410 direct/yr1
Risk of Cancer in Childhood Associated with Medical Imaging **$10,600,000 total**

Retrospective cohort across large integrated health care systems to assess imaging in pregnant women and children and to quantify the risk of childhood and adolescent cancer associated with these exposures.

PI (co-PI with Gould, Kaiser Foundation Research) 4/01/2015- 03/30/2020
PCORI
Pragmatic Trial of More versus Less Intensive Strategies for Surveillance of Patients with Small Pulmonary Nodules **$14,458,936 total**

Prospective comparative effectiveness study across 15 health care systems to compare different strategies for the surveillance of lung nodules. The study is novel in that patients will be recruited with routine clinical care at imaging and the creation of systematic quality improvement strategies to ensure no loss to follow up.

Past

PI 10/01/2010 - 09/30/2013
AHRQ $4,830,368 direct/yr1
RCT of US versus CT for Patients with Suspected Renal Colic **$9,210,000 total**

15 Center randomized pragmatic comparative effectiveness trial comparing different strategies for imaging patients with suspected kidney stones. The study exceeded enrollment and follow up targets, and the primary results were published in the NEJM in 2014. Many additional analyses are ongoing using these data.

PI 09/01/2008 - 07/31/2015
NIH K24 $172,000 direct/yr1
Mid-Career Development Award: Risk of Cancer Associated with Incidental Findings **$868,632 total**

PI 07/01/2011 - 07/01/2014
University of California Office of the President, CHQI $250,000 direct/yr1
Standardization and Optimization of CT Radiation Dose **$750,000 total**

Across the University of California Medical Centers.
Five-center observational study to collect radiation data across the five University of California campuses using automated techniques, analyze the sources of variation in dose, and conduct quality improvement initiatives to standardize practice

PI 09/30/2012 - 09/29/2014
CDC (Centers for Disease Control and Prevention) $250,000 direct/yr1
PEDS CT-DOSE: Pediatric CT Dose Optimization and Standardization Endeavor **$500,000 total**
Ten center observational study to collect radiation data and create benchmarks in children

Co-Investigator (PI Solberg, Health Partners) 07/01/2012 - 06/30/2014
PCORI (Patient Centered Outcomes Research Institute) $250,000 direct/yr1
Measuring Patient Outcome from High Tech Imaging Studies **$500,000 total**

Mixed methods study to understand imaging use, positive rates of imaging and patient perspectives on imaging, with respect to identifying patient centered outcomes important to patients.

PI 04/01/2009 - 03/31/2011
NIH / R21 **$317,000 total**
Risk of Cancer with Incidental Findings Identified on US Imaging

Retrospective cohort to understand cancer risks of incidental findings

PI
NIH / R21 09/01/2008 - 08/31/2010
Radiation Exposure from Imaging: are Doses in a Carcinogenic Range **$317,000 total**

Retrospective cohort to understand use of medical imaging within integrated health care systems

PI 10/01/1999 - 07/01/2005
DOD **$725,515 total**
Outcomes of Screening Mammography in Elderly Women

Medicare Data were analyzed to determine utilization of mammography and factors influencing survival

PI
NIH K07 09/01/1999 - 06/01/2005
Outcomes of Screening Mammography in Elderly Women **$635,687 total**

NIH Career development award to study breast cancer screening among elderly women.

PI
California Breast Cancer Research Program 07/01/2003 - 02/01/2007
Racial Disparity in Breast Cancer Mortality **$583,287 total**

Retrospective cohort to understand the causes for racial disparity in breast cancer outcomes

Co-Investigator (PI Kerlikowske UCSF) 04/01/2000 - 03/31/2005
NIH, U01 **$3,100,000 total**
San Francisco Mammography Registry: A Research Resource

Dr. Smith-Bindman project lead on 1) Physician Predictors of Mammography Accuracy and 2) Validation of the Medicare Screening Algorithm

Co-Investigator (PI – McCune, UCSF)
NIH 09/30/2006 - 06/30/2011
Clinical and Translational Science Institute (CTSI)

The grant is to enhance training and infrastructure across UCSF. I participate in the Biomedical Informatics Program to educate trainees about imaging, epidemiology and study design

Co-Investigator (PI- Lu, UCSF)
NIH **04/01/2006 - 03/01/2009**
Statistical Methods for Evaluation and Validation of Tests

Co-Investigator (PI Tlsty, UCSF)) 10/01/2005 - 09/30/2010
NIH
Biological Basis of Breast Density and Breast Cancer Risk

Co-Investigator (PI Esserman, UCSF) 05/01/2003 - 04/30/2007
Department of Defense/USAMRC **$6,900,000 total**
Blueprint for Regional Excellence in Breast Cancer Care

PI 01/01/2002 - 12/01/2006
Women's Health Research Center, UCSF **$70,000 total**
Down Syndrome Screening in the US

PI 04/01/2001 - 04/01/2003
Society of Radiologists in Ultrasound $**40,000 total**
Prenatal Ultrasound for Detection of Birth Defects and Chromosome Abnormalities

PI
Society of Radiologists in Ultrasound 04/01/2001 - 04/01/2004
Physician Variation in Ultrasound Accuracy **$30,000 total**

PI 07/01/2000 - 06/01/2001Radiologic
Society of North America **$40,000 direct/yr1**
U.S. U.K Comparison of The Accuracy of Screening Mammography

P
I 07/07/1999 - 06/01/2000
Radiologic Society of North America **$35,000 direct**
Prenatal diagnostic ultrasound for the detection of chromosomal Abnormalities

MOST SIGNIFICANT RESEARCH PUBLICATIONS

1) Smith-Bindman et al. Endovaginal ultrasound to evaluate endometrial abnormalities JAMA 1999 *Vaginal bleeding affects 7% of post-menopausal women, and historically women have undergone an invasive endometrial biopsy to exclude a diagnosis of cancer. This meta-analytic review found that endovaginal ultrasound is an easily tolerated non-invasive test that is accurate for the diagnosis of cancer, so that most women can avoid the need for an endometrial biopsy if they have a normal ultrasound test result. These results have been integrated into clinical practice guidelines in the US, Scotland, England, Germany, and Hong Kong. The publication has been cited 427 times based on SCOPUS accessed in 2015.*

2) Smith-Bindman et al. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA. 2001. *Prenatal ultrasound is widely used to screen for Down syndrome, but the impact on patients has not been well studied. This meta-analytic review suggests that the use of ultrasound for the detection of fetuses affected by Down syndrome may be associated with more harm than benefit, as it can lead to large numbers of unnecessary amniocenteses and subsequent fetal losses with little evidence of benefits. This article was accompanied by extensive media coverage (AP, Reuters, NY Times), and controversy, and prompted discussion regarding the role of ultrasound in prenatal diagnoses. The manuscript has been cited 217 times based on SCOPUS accessed in 2015.*

3) Smith-Bindman R et al. US-UK Comparison of Screening Mammography. JAMA 2003. *Screening mammography is an imprecise test, and there are considerable differences between physicians and programs in the accuracy of screening. This international comparison of screening mammography described 5.5 million mammograms obtained between 1996 to 1999 within three large-scale mammography registries or screening programs. Recall rates and open surgical biopsy rates were twice as high in the U.S. as in the U.K., although cancer rates were nearly identical. There was extensive media coverage (AP, Reuters, NY Times, Wall Street Journal, National Public Radio). These results have been widely cited, and were included in the IOM Report, "Saving Women's Lives." The publication was cited 223 times based on SCOPUS accessed in 2015.*

4) Smith-Bindman et al. Physician Predictors of Mammographic Accuracy. J Natl Cancer Inst 2005. *Beyond the issues raised about the collective quality of mammographic screening in the United States, even more pronounced concern is the glaring variation among U.S. physicians in the ability to accurately interpretation their patients' mammograms. Dr. Smith-Bindman studied the accuracy of mammographic screening among 208 U.S. physicians, who collectively interpreted 1.2 million mammograms, and she found extraordinary variation in the interpretive abilities of radiologists; the sensitivity spanned 29% to 97%, while the false positive rate (the percentage of women who did not have cancer, but who underwent additional diagnostic testing or biopsy at their physician's recommendation) ranged from 1 to 29%. The difference in accuracy was principally due to differences in their training, experience and dedication to screening mammography; in short, the more experienced mammographers - and those who read more than the minimum number of mammograms required by MQSA guidelines - did substantially better. These findings have already been integrated into the Institute of Medicine's report on Mammography Quality Standards, regarding Enhancement of Interpretative Performance. The manuscript was cited 82 times based on SCOPUS accessed in 2015.*

5) Smith-Bindman et al. Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med, 2006 *Racial and ethnic minorities tend to have larger, more advanced stage breast cancers at diagnosis than white women, and African American women have significantly higher breast cancer mortality. It has not been clear, however, if this is due to inherent differences in biology or the utilization of screening mammography. This paper sought to disentangle whether biology or the use of screening was largely responsible for the known racial and ethnic differences in breast cancer. This study was*

unique in that detailed cancer information was available from tumor registries that were linked with detailed information regarding mammography utilization. The results were striking. Most of the racial and ethnic differences in breast cancer features were reduced or eliminated after accounting for the frequency of mammography screening. The manuscript was cited 175 times on SCOPUS.

6) Smith-Bindman et al. Second trimester prenatal ultrasound for the detection of pregnancies at increased risk of Down syndrome. Prenat Diagn 2007 *Prenatal ultrasound is widely used to screen for Down syndrome, but the impact on patients has not been well studied. Our meta-analytic review found that ultrasound was not useful and this prompted our large prospective study which evaluated ultrasound in a larger cohort, including nearly 20,000 women, in whom nearly 500 had fetuses affected by Down syndrome. This large study confirmed these preliminary results. The manuscript was cited 51 times on SCOPUS.*

7) Smith-Bindman et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. JAMA Internal Medicine 2009 *This paper documented the variation in doses associated with routine CT. The widespread media attention that this paper received contributed to active policy discussion in this area. I was invited to present and discuss the results at the FDA, at a Congressional Hearing sponsored by the Health Subcommittee of the Committee on Energy and Commerce, and innumerable professional society meetings, and submitted (and had endorsed) a measure of quality around CT imaging by the National Quality Forum. The manuscript was cited 857 times based on SCOPUS accessed in 2015.*

8) Smith-Bindman R, Appendix F. Ionizing Radiation Exposure to the US Population, with a Focus on Radiation from Medical Imaging, in Breast and the Environment: A Life Course Approach. The Institute of Medicine. 2012 The IOM was commissioned to write a report on environmental causes of breast cancer. The Komen Foundation commissioned the report. I was asked to summarize what is known about the harmful effects of ionizing radiation on breast cancer risks. The IOM concluded that ionizing radiation is one of the largest, and the most preventable causes of breast cancer.

9) Miglioretti DL et al. Smith-Bindman senior author. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA Pediatr. 2013 Using a retrospective cohort design, this paper quantified the use of imaging among children within one of 7 large integrated health care systems, quantified the radiation exposure associated with these examinations, and estimated the likely impact of improved standardization of the conduct of CT on the risks of cancer. The manuscript concluded that if the top outlying radiation exposures could be reduced to the average (a modest goal) that 40% of expected cancer could be eliminated. *The manuscript was cited 150 times based on SCOPUS accessed in 2015*

10) Smith-Bindman R, et al. Risk of Thyroid Cancer based on Thyroid Ultrasound Imaging Characteristic: Result of A Population Based-Study. JAMA Internal Medicine. 2013. This retrospective observational study documented the risk of cancer associated with specific thyroid imaging findings. This is the first study that links a large cohort of patients with detailed imaging findings, with a comprehensive tumor registry to permit the quantification of the risk of cancer associated with specific findings. The results suggest that the number of biopsies can be reduced by up to 90%, with a relatively small impact on cancer detected. The results are being rapidly embraced by endocrinologists, surgeons and radiologists.

11) Smith-Bindman et al Ultrasound versus Computed Tomography for Suspected Nephrolithiasis NEJM. 2014. *This 15-center randomized comparative effectiveness study assessed whether ultrasound or CT should be the first imaging test in patients with suspected kidney stones. The study is unique in using a rigorous randomized trial design to assess a diagnostic imaging test, and in assessing a broad range of outcomes other than diagnostic accuracy. Emergency department patients with abdominal pain and suspected nephrolithiasis*

were randomly assigned to one of three arms for imaging: ultrasound performed by an emergency medicine physician, ultrasound provided by a radiologist, or computerized tomography (CT). No significant differences were observed over the next 6 months in rates of severe serious adverse events (SAEs), related SAEs, or total SAEs, or ED or hospital admission rates at 7 or 30 days; however, initial imaging with ultrasound was associated with lower 1 day and 6-month cumulative radiation exposures than initial imaging with CT. The manuscript was cited 45 times based on SCOPUS accessed in 2015

PUBLICATIONS

Peer Reviewed

1. Block JE, **Smith R**, Black D, Tenant HK. Does Exercise Prevent Osteoporosis? JAMA 1987 257:3115-3117.

2. Genant HK, Block JE, Steiger P, Glueer CC, **Smith R.** Quantitative Computed Tomography in Assessment of Osteoporosis. Sem in Nuclear Med 4 1987:316-333.

3. Genant HK, Steiger P, Block JE, **Smith R**, Black D, Ettinger B, Harris ST. Rate of change in bone mineral content as measured by QCT, DPA and SPA in postmenopausal women. J Bone Miner Res 1987 25; 212.

4. Ettinger B, Block JE, **Smith R,** Cummings SR, Harris ST, Genent HK. An examination of the association between vertebral deformities, physical disabilities and psychosocial problems. Maturitas 1988 10:283-96.

5. Block JE, **Smith R**, Glueer CC, Steiger P, Ettinger B, Genant HK. Models of Spinal Trabecular Bone Loss as Determined by Quantitative Computed Tomography. J Bone Miner Res 1989 4:249-57.

6. **Smith-Bindman R**, Cummings SR, Steiger P, Genant HK. A comparison of morphometric definitions of vertebral fractures. J Bone Miner Res 1991 6:25-34.

7. **Smith-Bindman R**, Steiger P, Cummings SR, Genant HK. The Index of Radiographic Area (IRA): a new approach for estimating the severity of vertebral deformity. Bone and Mineral 1991 15:137-50

8. **Smith-Bindman R**, Kerlikowske K, Feldstein V, Subak L, Scheidler J, Segal M, Brand R,Grady D. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities: a meta- analytic review. JAMA 1998 280:1510-1517

9. **Smith-Bindman, R**, Kerlikowske K, Feldstein V. Endovaginal ultrasound to evaluate endometrial abnormalities. JAMA 1999 281:1693-4.

10. Vincoff N, Callen P, **Smith-Bindman R**, Goldstein R. Effect of transducer frequency on the appearance of the fetal bowel. J Ultrasound Med 1999 18:799-803

11. **Smith-Bindman R**, Gebretsadik T, Kerlikowske K, Newman J. Is screening mammography effective in elderly women? Am J Med 2000 108:112-118, 2000

12. **Smith-Bindman R**, Hosmer W, Feldstein VA, Deeks JJ, Goldberg JD. Second-trimester ultrasound to detect fetuses with Down syndrome: a meta-analysis. JAMA 2001 285 (8):1044-55.

13. **Smith-Bindman R**, Hosmer W, Coppanigro M, Cunningham G. The variability in the interpretation of prenatal diagnostic ultrasound. Ultrasound Obstet Gynecol 2001 17:(4):326-332.

14. Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, Fleischer AC,Goldstein SR, Hunt RB, Kurman RJ, Kurtz AB, Laing FC, Parsons AK, **Smith-Bindman R**, Walker J.Evaluation of woman with postmenopausal bleeding: Society of Radiologists in Ultrasound Consensus Conference Statement. J Ultrasound Med 2001 20 10;1025-1036.

15. **Smith-Bindman R**, Feldstein V, Goldberg JD. The Genetic Sonogram in Screening for Down Syndrome, J Ultrasound Med 2001 (20);1153-5.

16. **Smith-Bindman R**, Chu P, Ecker J, Feldstein V, Filly R, Bacchetti P. US evaluation of fetal growth: prediction of neonatal outcomes. Radiology 2002 223(1):153-161.

17. Shepherd JA, Kerlikowske K, **Smith-Bindman R**, Genant H, Cummings SR. Measurement of breast density with dual X-ray absorptiometry: feasibility. Radiology 2002 223(5): 554-557.

18. Prevrhal S, Shepherd JA, **Smith-Bindman R**, Kerlikowske K, Cummings SR. Accuracy of Mammographic Breast Density analysis: Results of Formal Operator Training. J Cancer, Epi. Bio. & Prev 2002 11(11); 1389-93.

19. **Smith-Bindman R**, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, Bobo JK, Lee NC, Wallis MG, Patnick J, Kerlikowske K. Comparison of Screening Mammography in the US and the UK. JAMA 2003 290(16):2129-37.

20. **Smith-Bindman R**, Chu P, Bacchetti P, Waters JJ, Mutton D, Alberman E. Prenatal screening for Down syndrome in England and Wales and population-based birth outcomes. Am J Obstet Gynecol 2003 189(4):980-5.

21. **Smith-Bindman R**, Chu P, Ecker J, Feldstein V, Bacchetti P, Filly R. Adverse birth outcomes in relation to prenatal sonographic measurements of fetal size. J Ultrasound Med 2003 Apr 22:347-356.

22. Kerlikowske K, **Smith-Bindman R**, Barclay J, Ling BM, Grady D. Evaluation of Abnormal Mammography Results and Palpable Breast Abnormalities. Ann Intern Med 2003 139(4):274-84.

23. Ziv E, Shepherd J, **Smith-Bindman R** Kerlikowske K. Mammographic Breast Density and Family History of Breast Cancer. J Natl Cancer Inst 2003 95(7) 556-558.

24. **Smith-Bindman R**, Weiss E, Feldstein V. How thick is too thick? What endometrial thickness should prompt biopsy in an asymptomatic postmenopausal woman? Ultrasound Obstet Gynecol, 2004 June; 24:558-565

25. **Smith-Bindman R**. Diagnostic Imaging in the Differential Diagnosis of Vaginal Bleeding and Breast Mass. Adv Stud Med 2004 (9):476-482.

26. Ziv E, Tice J, **Smith-Bindman R**, Shepherd J, Cummings S, Kerlikowske K. Mammographic density and estrogen receptor status of breast cancer. Cancer Epidemiol Biomarkers Prev 2004 13 (12):2090-5

27. Benn PA, Egan JF, Fang M, **Smith-Bindman R**. Changes in the utilization of prenatal diagnosis. Obstet Gynecol 2004 103(6):1255-60.

28. **Smith-Bindman R**, Chu P, Miglioretti D, Quale C, Rosenberg R, Cutter G, Geller B, Bacchetti P, Sickles E, Kerlikowske K. Physician Predictors of Mammographic Accuracy. J Natl Cancer Inst 2005 97:358-67

29. Kerlikowske K, **Smith-Bindman R**, Abraham LA, Lehman CD, Yankaskas BC, Ballard Barbash R, Barlow WE, Voeks JH, Geller BM, Carney PA, Sickles EA. Breast Cancer Yield for Screening Mammographic Examinations with Recommendation for Short-Interval Follow-up. Radiology 2005 234(3):684-692.

30. **Smith-Bindman R**, Ballard-Barbash R, Miglioretti D, Patnick J, Kerlikowske K. Comparing the Performance of Mammography Screening in the United States and the United Kingdom. J Med Screen 2005 12(1): 50-54.

31. Sickles EA, Miglioretti D, Ballard-Barbash R, Geller B, Leung J, Rosenberg R, **Smith-Bindman R**, Yankaskas B. Performance Benchmarks for Diagnostic Mammography. Radiology 2005 235(3):775-90

32. Kerlikowske K, Creasman J, Leung JW, **Smith-Bindman R**, Ernster VL. Differences in screening outcomes among White, Chinese, and Filipino women. Arch Intern Med. 2005 165(16):1862-8

33. Haggstrom DA, Quale C, **Smith-Bindman R**. Differences in the Quality of Breast Cancer Care Among Vulnerable Populations. Cancer. 2005 Dec 1;104(11):2347-58.

34. **Smith-Bindman R**, Miglioretti D, Lurie N, Abraham L, Ballard Barbash R, Strzelczyk J, Dignan M, Barlow W, Beasley C, Kerlikowske K. Does Utilization of Screening Mammography Explain Racial and Ethnic Differences in Breast Cancer? Ann Intern Med, 2006 144(8):541-53.

35. **Smith-Bindman R**, Quale C, Chu PW, Rosenberg R, Kerlikowske K. Can Medicare Billing Claims Data Be Used to Assess Mammography Utilization Among Women Age 65 and Older. Medical Care 2006 44(5):463-70

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Exhibit B

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Exhibit C

Rebecca Smith-Bindman Compensation and Prior Testimony

Dr. Smith-Bindman's fees are $1,000/hr. She has not testified in other cases during the previous four years.